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COMMENTARY

Does volume expansion in pre-eclampsia help or hinder?

It is not yet clear, whether, or in what circumstances, plasma expansion in pre-eclampsia is helpful, or even harmful. In this issue of the Journal (p. 634) Belfort *et al.* present some hard-won data from South Africa relating to central cardiopulmonary changes, showing that plasma expansion, preceded or followed by vasodilatation, was safe in their hands. However, at least in some women, there were dramatic central cardiovascular changes and these merit some consideration.

Cerebral oedema or haemorrhage, cardiac failure and pulmonary oedema are ever-present hazards of pre-eclampsia (or eclampsia) which are still significant causes of maternal mortality. In the fulminating phase of pre-eclampsia, study of the cardiovascular events tends to be confounded by the overriding necessity to treat the condition. Over the last 15 years or so, this pragmatic approach has extended to include volume expansion (Cloeren *et al.* 1973; Sehgal & Hitt 1980).

The central haemodynamic status of most women with severe pre-eclampsia is thought to comprise a hyperdynamic left ventricle, a variably increased systemic vascular resistance and normal pulmonary vascular resistance (Clark *et al.* 1986). But left ventricular function depends on systemic resistance and can range widely from a high output state with a modest increase in systemic resistance to a low output state, with or without failure, and an extreme rise in systemic resistance. The findings of Belfort *et al.* seem to confirm this and a few of their 10 women had a very low cardiac index and very high systemic resistance. These women did not stand out clinically in any way, so that without the cardiac catheter their different cardiovascular status would not have been recognized. These are the women who would seem to have the most to gain from plasma expansion provided there is concomitant vasodilatation and provided there is sufficient surveillance to detect or treat overload.

The notion of pharmacological vasodilatation of the arterial circulation and volume expansion is an appealing one, seeming to counter the effects if not the cause of the condition. It overthrows the traditional caution concerning fluid infusion in the acute phase of pre-eclampsia based on recognition of a contracted arterial system already under high pressure. On the other hand, constraint in fluid infusion is already abandoned when pre-load for lumbar epidural analgesia and management of blood loss or coagulopathy are required. The question therefore is often not whether to give fluid but what, how much, how fast and with what safeguards.

As Belfort and colleagues point out, information about cardiac output (or index) in severe pre-eclampsia is confused (for references see also Benedetti 1982), and there is no consistent difference from normotensive pregnant women. It varies widely between women and it is probably different at different stages of the disorder. Cardiac output has certainly been shown to be raised in some circumstances (Rafferty & Berkowitz 1980) although in this, as in some other studies, prior therapy confounds. The dramatic increase from initially low values with modest plasma expansion in the South African study before other therapy provides some insight into the instability of the circulation at this time and the pitfalls of cross-sectional data.

One of the possible benefits from increased cardiac output and blood volume expansion is increased placental perfusion and improved fetal growth. Improved placental perfusion, as judged by increased radioactive clearance during plasma expansion therapy (Cloeren *et al.*

1973), has been described. Although a comparative reduction in plasma volume has certainly been described in pre-eclampsia (Soffronoff *et al.* 1977), it should be appreciated that in severe pre-eclampsia the fetus also tends to be small and the lesser increases in plasma volume are associated with small-for-gestational-age infants with poorer outcome (Arias 1975). In pre-eclamptic primigravidae with average-sized babies a reduction in plasma volume has not been found (MacGillivray & Campbell 1986). At the very least, therefore, it should be clear that the notion of long-term plasma expansion is not addressing the cause of the failure of fetal growth. Although an increase in serum albumin and colloid osmotic pressure can be obtained, the effect is transitory and an improvement in intervillous blood flow could not be demonstrated 1 h after albumin infusion (Jouppila *et al.* 1983). The therapeutic options for long-term treatment seem increasingly limited as earlier delivery becomes more feasible. There is still a time of fetal compromise with severe but manageable pre-eclampsia between about 24 and 28 weeks when plasma expansion could possibly be of value. We await a randomized trial showing benefit.

The topic of the paper by Belfort and colleagues relates more to the acute cardiopulmonary events, and the findings are relevant to our understanding of management during labour and delivery. It does not appear that modest and controlled volume expansion aggravates the hypertension of pre-eclampsia. Acute volume load has been shown previously to be associated with a reduction in mean blood pressure (Gallery *et al.* 1980) though in the South African study a fall in pressure occurred only with vasodilatation.

An important question is whether volume expansion promotes or protects against pulmonary oedema. There is a recognized reduction in colloid osmotic pressure in severe pre-eclampsia compared with both non-pregnant and normotensive pregnant women (Benedetti & Carlson 1979). There are three possible mechanisms for pulmonary oedema: increased pulmonary artery hydrostatic pressure, abnormal capillary permeability and reduced colloid osmotic pressure (Benedetti 1982).

Any or several of these mechanisms may occur. In a 4-year experience of pulmonary oedema in severe pre-eclampsia, Benedetti *et al.* (1985) found that a combination of reduced colloid osmotic pressure and increased hydrostatic pulmonary pressure (measured as an increase in pulmonary artery wedge pressure) was the commonest combination of factors. In this, as in many other studies, vigorous treatment has often preceded investigation. Where capillary permeability is increased (and this would be certain only when invasive monitoring showed a normal pulmonary artery wedge pressure and normal heart function in the presence of pulmonary oedema) then colloid infusion would be expected to make this worse by increasing the extracellular colloid osmotic pressure.

Measurement of pulmonary artery wedge pressure gives crucial information and improves understanding. Usually, in severe pre-eclampsia it is normal or low and in this situation with good left ventricular function and high systemic resistance, volume infusion seems to permit some vasodilatation and improve at least renal perfusion (Clark *et al.* 1986). However, if pulmonary arterial wedge pressure is raised and especially if left ventricular function is impaired, volume restriction is required at least until vasodilatation is effected. Central venous pressure does not correlate with pulmonary artery wedge pressure when CVP is greater than 6 mmHg (Benedetti 1982) so is of value only when levels are below this. When colloid osmotic pressure is low a very small rise in pulmonary arterial wedge pressure can result in pulmonary oedema. It thus seems that blind volume expansion is potentially dangerous.

Much of the pulmonary oedema, when it occurs, does so postpartum. There is substantial reduction of colloid osmotic pressure after delivery (Moise & Cotton 1985). This may be aggravated by the supine position, blood loss and infusion of crystalloids. Immediately at delivery (Benedetti *et al.* 1985) there may be a fall in blood pressure in the anaesthetized pre-eclamptic woman, and if the temporary nature of this fall is not recognized, vigorous fluid replacement can result in fluid overload.

The findings from South Africa show that an increase in cardiac index can be effected by vasodilatation alone, although an additional increase was obtained by volume expansion. The duration and therapeutic benefit of this increase is uncertain. At the very least, it can be argued that, wherever possible, treatment of the ill woman with severe pre-eclampsia should take place only where high dependency care can be provided with invasive monitoring if required.

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Haemodynamic changes in gestational proteinuric hypertension: the effects of rapid volume expansion and vasodilator therapy

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Summary. Ten patients with gestational proteinuric hypertension were studied with a Swan–Ganz thermodilution haemodynamic catheter before, during and after plasma volume expansion. Five patients were treated with dihydralazine before volume expansion and five after volume expansion. Before treatment all patients had a low pulmonary capillary wedge pressure (PCWP), low cardiac index (CI) and high systemic vascular resistance (SVR). Following volume expansion the PCWP and CI increased, the SVR decreased but the blood pressure (BP) was unchanged. Administration of dihydralazine following volume expansion led to a decrease in PCWP, an increase in CI and a decrease in SVR and BP. Dihydralazine alone caused an increase in heart rate, PCWP, and CI, and a decrease in SVR and BP. Volume expansion, by increasing CI and decreasing SVR, may be of therapeutic benefit in the severely hypertensive pregnant patient with a low cardiac index.

The use of the Swan–Ganz thermodilution haemodynamic catheter is an accepted procedure in the management of the severely hypertensive pregnant patient (Clark *et al.* 1985). There is, however, considerable uncertainty as to the initial untreated baseline haemodynamic characteristics in severe hypertension in pregnancy. Most reports suggest that the cardiac index (CI) and systemic vascular resistance (SVR) are elevated or within the normal range for pregnancy (Phelan & Yurth 1982; Benedetti *et al.* 1980; Kusniar *et al.* 1986; Rafferty & Berkowitz 1980; Easterling *et al.* 1986; Lee *et al.* 1986). Most studies have been on women in labour (Rafferty & Berkowitz 1980) or postpartum (Phelan & Yurth 1982) or else in patients who have been given fluid or vasodilator agents before the initial measurements were made (Benedetti *et al.* 1980). There have been few reports of studies of untreated hypertensive proteinuric patients who had not received either intravenous infusions or a low sodium diet (Groenendijk *et al.* 1984) before the initial baseline measurements were made. Observations on treated patients cannot be considered to be indicative of the true haemodynamic state of patients with gestational proteinuric hypertension (pre-eclampsia). There is also little information on the effect of plasma volume expansion in untreated patients. The objectives of the present study were to determine the baseline haemodynamic characteristics in patients with untreated severe gestational proteinuric hypertension (pre-eclampsia), and to investigate

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the effects of plasma volume expansion and of intravenous hydralazine, with and without prior volume expansion, in these patients.

Patients and methods

Ten Cape coloured or black patients with pre-eclampsia, defined in accordance with the criteria recommended by the International Society for the Study of Hypertension in Pregnancy (Davey & MacGillivray 1986), were studied. All the patients had severe hypertension with a blood pressure in excess of 160/110 mmHg and significant proteinuria of 1 g/l or more; none was known to have pre-existing hypertension, renal disease or heart disease. They had been admitted as emergencies to the Groote Schuur Hospital Maternity Centre with live fetuses; no patient was on a sodium-restricted diet or had taken any anti-hypertensive medication (including diuretics) before admission and none was in labour at the time of the initial measurements. Four of the patients were judged to have 'imminent eclampsia' and had been started on a magnesium sulphate infusion before insertion of the Swan–Ganz catheter but none of these patients had received more than 100 ml of intravenous fluid before the initial haemodynamic measurements. The Swan–Ganz catheter was inserted under local anaesthesia and no sedative drugs were used. The following laboratory tests were done on admission and at the end of the monitoring period: serum urea, creatinine, uric acid, liver function tests, full blood count, coagulation screen (including platelet count, fibrin degradation products, prothrombin index and partial thromboplastin time) and a routine reagent strip urine analysis. All patients had electrocardiograms which did not show any clinically significant change after the investigation.

The study was approved by the ethics and research committee of the University of Cape Town Medical School, and all patients gave free informed written consent. The haemodynamic monitoring was recorded in the obstetric intensive care unit under the direct supervision of the investigators. In 8 of the 10 patients the Swan–Ganz catheter was inserted by the principal author (M.B.) and in the other two cases by a co-author of the study (P.U.), a specialist anaesthetist.

A Swan–Ganz radio opaque thermodilution flow-directed catheter was inserted under continuous pressure monitoring through a Cordis introducer placed in the R internal jugular vein. The position of the catheter tip was confirmed by a single chest radiograph. All measurements were taken with the patient in a 15° L lateral tilt. The zero reference mark was fixed at 5 cm below the third intercostal space in the mid-axillary line. Cardiac output was measured in triplicate by the thermodilution technique with a 10 ml injectate of 0·9% NaCl at 0°C and was calculated by a cardiac output analogue computer (Edwards Laboratories, Irvine, California). The peripheral blood pressure was continuously recorded from an arterial line placed in the radial artery and the finding of severe hypertension was confirmed before the Swan–Ganz catheter was inserted. All measurements were repeated hourly and after any change in the patient's condition. The catheters were continuously flushed with a small volume of normal saline containing heparin (1000 u/200 ml). Baseline measurements were taken at least 30 min after catheter insertion and before surgical induction of labour to allow stabilization of the haemodynamic state. All equipment was regularly calibrated throughout each study. If labour was induced all subsequent readings were taken between uterine contractions.

Patients were randomly allocated to one of two treatment groups following the baseline determinations. Group A patients were given 200 ml of 3·5% colloid plasma substitute (Haemaccel–Hoechst) to produce a small but rapid expansion of blood volume Successive 200 ml volumes of Haemaccel were then infused, each over 30 min until the pulmonary capillary wedge pressure (PCWP) had increased to a minimum of 16 mmHg and haemodynamic measurements were performed at the end of each aliquot infusion. Once the PCWP had been raised to ≥16 mmHg, dihydralazine was infused (25 mg/200 ml normal saline) at a rate sufficient to maintain the diastolic blood pressure (DBP) between 90 and 100 mmHg. Group B patients were treated with dihydralazine in an identical manner but without prior Haemaccel or intravenous fluid infusion. After the initial measurements and the infusion of Haemaccel and dihydralazine had been completed, magnesium sulphate infusion (at a rate of 1 g/h) was started in the six patients not already on therapy. The magnesium sulphate infusion was discontinued if the urine output fell below 50 ml/h All patients received standard obstetric care and

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had continuous fetal heart rate monitoring throughout the study period. The changes in the haemodynamic variables were analysed by paired *t*-test. The observations on Group A given Haemaccel and dihydralazine and Group B given dihydralazine alone were compared by unpaired *t*-test.

Results

The clinical characteristics and the baseline haemodynamic measurements on the individual patients are shown in Tables 1 and 2.

Those patients who had already been started on an infusion of magnesium sulphate before baseline values were recorded are indicated in Table 2. Analysis by unpaired Student's *t*-test of pulse rate, systolic and diastolic pressures, cardiac index, pulmonary capillary wedge pressure and right atrial pressure did not show any significant differences between these two groups. For this reason the results of the 10 patients have been considered together.

Seven patients were delivered by caesarean section, one was delivered by vacuum extraction and two had normal vaginal deliveries following surgical induction of labour. Pregnancy outcome is summarized in Table 3.

There were no complications related to the use of the Swan–Ganz catheter. One of the patients who had a normal vaginal delivery developed a postpartum vulval haematoma which required evacuation under general anaesthesia. The mean age of the patients was 23·8 years (range 17–30) and the mean gestational age was 34·3 weeks (range 28–40). The mean arterial pressure (MAP) on admission was 143·7 mmHg (range 132·6–150·7) and the mean DBP was 114·1 (range 110–122). The mean systemic vascular resistance (SVR) was 2392 dyn.s.cm^{-5} (range 1448–4168) and two of the patients had SVR values that are amongst the highest yet reported in pregnancy hypertension, 3839 and 4168 dyn.s.cm^{-5} respectively. The cardiac indices (CI) in these two patients were extremely low, 1·78 l/min/m^2 and 1·47 l/min/m^2 respectively. The mean CI of the 10 patients before commencing treatment was 3·01 l/min/m^2. This value is appreciably less than that found in normal pregnant patients by Rose *et al.* (1956) who reported a mean CI of between 3·93 l/min/m^2 at 28–30 weeks and 3·44 l/min/m^2 at 36–40 weeks. Groenendijk *et al.* (1984) reported the mean CI to be 4·53 l/min/m^2 in four normal pregnant patients, and 2·75 l/min/m^2 in 10 hypertensive patients but all had been on sodium-restricted diets.

Table 4 shows the results of the infusion of Haemaccel. In all patients the infusion was completed within 90 min and not more than 600 ml of the fluid was needed to raise the PCWP to 16 mmHg. In one patient the PCWP rose from 5 to 23 mmHg following the initial 200 ml Haemaccel infusion. None of the patients experienced respiratory difficulty or had clinical or radiological evidence of pulmonary oedema. In six of the 10 patients pulmonary shunt before and after treatment was calculated, but because

Table 1. Individual patient data and laboratory findings

Patient no.	Race†	Age (years)	Gravidity	Body surface area (m^2)	Gestational age (weeks)	Proteinuria‡	Hb (g/dl)	PCV (%)	Urea (mmol/l)	Creatinine (μmol/l)	Uric acid (mmol/l)	Platelet count (×10^3/l)
1*	C	20	1	1·51	35	4+	14·2	0·41	4·6	79	0·45	241
2*	C	19	2	1·54	34	4+	11·5	0·33	4·3	85	0·40	131
3	C	28	3	1·86	40	4+	10·5	0·31	3·2	68	0·48	150
4*	C	28	3	1·64	28	3+	11·7	0·34	5·0	97	0·35	135
5*	B	24	2	1·76	34	4+	14·4	0·37	4·8	99	0·61	120
6	B	28	3	1·83	32	3+	11·7	0·33	2·9	62	0·39	272
7	B	23	1	1·80	39	4+	10·5	0·30	2·1	62	0·31	202
8*	B	30	3	1·99	32	4+	13·4	0·39	3·2	79	0·35	289
9	B	21	2	1·70	32	4+	14·9	0·43	2·9	106	0·34	233
10	C	17	1	1·68	37	4+	12·0	0·36	5·7	62	0·41	138
Mean		23·8	2·1	1·7	34·3		12·5	0·36	3·8	79·9	0·41	191
(SD)		4·5	0·87	0·14	3·6		1·6	0·04	1·2	16·6	0·08	63·9

* Volume-expanded group.

† B, black Xosa patient; C, so-called 'coloured' patient.

‡ Proteinuria on admission (multistix Ames).

Hb, Haemoglobin; PCV, haematocrit.

Table 2. Baseline haemodynamic values before volume expansion or vasodilator therapy

Patient	Pulse	Blood pressure (mmHg)				CI	PCWP	RAP	SVR	PVR	SVI	LVSWI	RVSWI
no	(bts/min)	S	D	PS	PD	(l/min/m^2)	(mmHg)	(mmHg)	(dyn s cm^{-5})	(dyn s cm^{-5})	(l/min/m^2)	(g/min/m^2)	(g/min/m^2)
*1	92	180	110	24	12	3·31	10	2	2087	96	36	60	7
*2	111	200	113	12	0	3·29	4	0	2230	0	30	55	2
3	99	201	110	30	10	3·01	7	0	2052	138	32	60	7
*4†	84	211	112	22	8	3·90	4	4	1760	108	46	89	6
*5†	102	212	120	24	6	1·78	0	0	3839	306	17	36	3
6†	92	212	111	26	9	1·47	9	4	4168	168	16	30	2
7†	104	185	115	37	4	3·11	4	0	2116	157	30	59	6
*8	91	200	117	32	17	3·95	5	2	1448	173	43	82	12
9	83	189	111	22	7	3·41	2	0	1868	136	42	76	7
10	73	204	122	27	8	2·88	7	5	2352	119	39	77	5
Mean	93	199	114	26	8	3·01	5	2	2392	140	33	62	6
(SD)	11	11	4	7	5	0·81	3	2	890	76	10	19	3

* Volume-expanded group

† Patients on magnesium sulphate at time of initial readings

S, Systolic; D, diastolic, PS, pulmonary systolic; PD, pulmonary diastolic, CI, cardiac index; PCWP, pulmonary capillary wedge pressure, RAP, right atrial pressure; SVR, systemic vascular resistance, PVR, pulmonary vascular resistance, SVI, stroke volume index; LVSWI, left ventricular stroke work index, RVSWI, right ventricular stroke work index.

of technical difficulties the data cannot be regarded as reliable and have not been included in this analysis. The problem of increased pulmonary shunt with volume expansion is being addressed in detail in current research.

Following volume expansion alone there was no significant change in pulse rate or in systolic, diastolic or mean arterial blood pressures. The CI, however, increased significantly from 3·2 (SD 0·8) to 4·6 (SD 0·8) l/min/m^2 (P<0·05). The stroke volume index (SVI) also increased significantly from 35 (SD 12) to 48 (SD 4) l/min/m^2 (P<0·05). The PCWP and right atrial pressure (RAP) increased significantly from 4·6 (SD 3·6) to 16·6 (SD 5·1) mmHg (P<0·005) and from 3·6 (SD 4·0) to 8·6 (SD 6·0) mmHg (P<0·02) respectively. The SVR decreased from 2273 (SD 926) to 1438 (SD 219) dyn.s.cm^{-5}. There were no significant changes in pulse rate or in left ventricular stroke work index (LVWSI) or right ventricular stroke work index (RVSWI).

It should be noted that although the CI and SVI increased and the SVR decreased following volume expansion, the blood pressure was unchanged. Subsequent infusion of dihydralazine, however, lowered the blood pressure and was associated with a further increase in CI from 4·6 (SD 0·8) to 5·3 (SD 1·3) l/min/m^2, an increase of 15%.

Infusion of 200–600 ml of Haemaccel increased the mean CI from 2·79 to 5·05 l/min/m^2 in the low CI group (81%) and from 3·24 to 4·59

Table 3. Pregnancy outcome and neonatal data

Patient no.	Mode of delivery	Sex	Gestational age (weeks)	Birthweight (g)	Apgar scores at 1 min/5 min
1*	C	M	35	1575	4/8
2*	NVD	F	34	2240	9/10
3	C	M	40	4375	3/7
4*	C	M	28	1020	3/5
5*	C	M	34	1350	3/6
6	C	F	32	1070	2/4
7	VE	M	39	2900	4/9
8*	C	F	32	1250	3/4
9	C	F	32	1580	1/7
10	NVD	M	37	2420	5/10

* Volume-expanded patients.

C, Caesarean section; NVD, normal vaginal delivery; VE, vacuum extraction.

Table 4. Haemodynamic variables before and after volume expansion and vasodilator therapy

	Initial (n=10)	Volume expansion only (n=5)			After volume expansion and vasodilation (n=5)		Vasodilation only (n=5)		
		Before	After	P		P	Before	After	P
Pulse (beats/min)	93 (11)	96 (10)	97 (11)	NS	120 (19)	0·005	90 (12)	102 (11)	0 01
BP (mmHg)									
Systolic	199 (11)	201 (13)	202 (13)	NS	158 (28)	0·01	198 (11)	173 (23)	0·005
Diastolic	114 (4)	114 (4)	112 (7)	NS	82 (15)	0·01	114 (5)	8 (9)	0·002
MAP	144 (6)	143 (7)	142 (8)	NS	107 (19)	0·01	143 (5)	112 (10)	0 005
CI (l/min/m^2)	3·01 (0·81)	3·2 (0 8)	4·6 (0 8)	0·05	5·3 (1·3)	0·02	2·79 (0 7)	3·95 (1)	0·002
SVI (l/min/m^2)	33 (10)	35 (12)	48 (4)	0·05	47 (12)	NS	56 (16)	71 (23)	0·02
PCWP (mmHg)	5 (3)	4·6 (3·6)	16 6 (5 1)	0 0005	12·6 (3·1)	0·0005	6 (3)	9 (3)	NS
RAP* (mmHg)	2 (2)	3·6 (4·9)	8·6 (6·0)	0·02	5·2 (5·0)	NS	3 (2)	5 (6)	0·005
SVR (dyn.s.cm^{-5})	2392 (890)	2273 (926)	1438 (219)	NS	987 (366)	0·02	2511 (942)	1375 (673)	0·005
PVR (dyn.s.cm^{-5})	140 (76)	136 (13)	48 (40)	NS	60 (34)	NS	144 (19)	65 (21)	0·0005
LVSWI (g/min/m^2)	62 (19)	64 (22)	83 (10)	NS	59 (16)	NS	59 (20)	55 (20)	NS
RVSWI (g/min/m^2)	6 (3)	6 (4)	9 (5)	NS	8 (4)	NS	6 (2)	5 (3)	NS

NS, not significant Results are given as means (standard deviations) *n*, Number of samples

* (Central venous pressure).

BP, Blood pressure, MAP, mean arterial pressure For other abbreviations see Table 2

l/min/m^2 overall (42%). This marked increase may explain the high CI reported in other series where intravenous fluids had often been started before the baseline readings were made. In the patients who had a very low initial CI the haemodynamic effect of the fluid infusion on the cardiac indices was proportionately greater than in those who had a normal initial CI (Table 5). There was also a proportionately greater decrease in the SVR and increase in the SVI. In the patients with initial cardiac indices within the normal range there were minimal changes in CI, SVR and SVI.

In Group A patients who were first treated with plasma volume expansion and then infused with dihydralazine the MAP decreased from 142 (SD 8) to 107 (SD 19) mmHg ($P<0{\cdot}01$) and the CI increased from 3·2 (SD 0·08) to 5·3 (SD 1·3) l/min/m^2 which was significantly greater than that with dihydralazine alone ($P<0{\cdot}02$). The decrease in the SVR in the volume-expanded dihydralazine-treated group was significantly greater than in the group treated with dihydralazine alone ($P<0{\cdot}02$).

In Group B patients given dihydralazine who were not preloaded with Haemaccel the DBP fell from 114 (SD 5) to 88 (SD 9) mmHG ($P<0{\cdot}002$) and the MAP fell from 143 (SD 5) to 112 (SD 10) mmHG ($P<0{\cdot}005$). The CI rose significantly from 2·79 (SD 0·7) to 3·95 (SD 1) l/min/m^2 ($P<0{\cdot}002$). The SVR decreased from 2511 (SD 942) to 1375 (SD 673) dyn.s.cm^{-5} ($P<0{\cdot}0005$).

After treatment, group A patients treated with plasma volume expansion and hydralazine had a significantly higher CI and PCWP ($P<0{\cdot}05$) and a significantly lower SVR ($P<0{\cdot}02$) than group B patients treated with dihydralazine alone.

Table 6 shows the individual patient data for the different groups as well as detailing the amount of fluid required in each patient. The response of the low cardiac index patients is again highlighted.

There was no relation between the initial central venous pressure (CVP) and the PCWP measurements (correlation coefficient −0·095). This finding supports the observation of Cotton *et al.* (1985) that measurements of CVP may be misleading as to the true haemodynamic state and underlines the value of haemodynamic monitoring with a Swan–Ganz catheter in patients with severe hypertension in pregnancy.

Discussion

Previous studies on cardiac output/index in gestational hypertension have reached various conclusions. Littler *et al.* (1973), Werko (1954), Groenendijk *et al.* (1984), Strauss *et al.* (1980) and Smith (1970) reported cardiac output to be lower in gestational hypertension than in normal pregnant patients. Assali *et al.* (1964) found no difference in the cardiac output between normal patients and patients who had gestational hypertension. Lee *et al.* (1986) found that the majority

Table 5. The effect of rapid volume expansion on the haemodynamic measurements following a 600-ml bolus of Haemaccel. The low initial cardiac index (CI) group (n=3) is compared with the normal initial CI group (n=2)

CI group	Before volume expansion	After volume expansion
Low (mean CI=2·8 (SD 0·9))		
CI (l/min/m^2)	2·8 (1·78–3·31)	5·1 (4·8–5·3)
Systemic vascular resistance (dyn.s cm^{-5})	2718 (3086–3839)	1351 (1227–1708)
Stroke volume index (l/min/m^2)	29 (17–36)	50 (38–52)
Normal (mean CI=3·9 (SD 0·1))		
CI (l/min/m^2)	3·9 (3·8–4·0)	3·7 (3·6–3·8)
Systemic vascular resistance (dyn.s.cm^{-5})	1604 (1384–1824)	1567 (1226–1908)
Stroke volume index (l/min/m^2)	45 (43–47)	45 (41–49)

Results are means (range).

of patients with gestational hypertension have a normal cardiac index, normal plasma volume and normal to elevated systemic vascular resistance compared with normal pregnant patients. In contrast, Hamilton (1950), Benedetti *et al.* (1980), Phelan & Yurth (1982), Kuzniar *et al.* (1986) and Easterling *et al.* (1986) all reported increased cardiac output in patients with gestational hypertension. Wasserstrum & Cotton (1986) have suggested that patients with gestational hypertension may fall into different pathophysiological categories or subsets and should be divided according to their haemodynamic findings. These subsets include those with low cardiac output/high systemic vascular resistance, and those with high cardiac output/low systemic vascular resistance. This division should, however, be regarded as tentative in view of the paucity of data in untreated subjects.

The discrepancies in the findings of different workers may be explained in a number of ways. One explanation is that in many, if not most, studies a variable amount of fluid had been infused intravenously before the initial observations were made. This particularly applies to investigations performed on patients in labour. In the present study there was a marked increase

Table 6. Individual patient data for the fluid expansion, fluid and vasodilator and vasodilator only groups

Treatment	Patient no.	Volume (ml)	MAP (mmHg)		CI (l/min/m^2)		SVR (dyn.s.cm^{-5})	
			Before	After	Before	After	Before	After
Volume expansion only . 200–600 ml Haemaccel	1*	400	132	133	3·31	5·36	2086	1251
	2*	600	141	149	3·29	5·81	2230	1450
	4	600	145	145	3·90	3·65	1759	1809
	5*	600	151	148	1·78	4·80	3839	1352
	8	200	145	137	3·95	3·83	1448	1349
Volume expansion followed by vasodilator	1		133	90	5·36	4·86	1251	980
	2		149	97	5·81	7·93	1450	617
	4		145	134	3·65	3·89	1809	1596
	5		148	97	4·80	5·10	1352	841
	8		137	119	3·83	4·75	1349	904
Vasodilator only	3		144	117	3·01	4·46	2052	1204
	6		145	127	1·47	2·06	4168	2524
	7		138	98	3·11	4·04	2116	997
	9		137	97	3·41	4·86	1868	812
	10		149	123	2·88	4·34	2352	1340

MAP, Mean arterial pressure; CI, cardiac index; SVR, systemic vascular resistance.
*Low initial cardiac index group.

in cardiac output after infusion of even small amounts of fluid, particularly in patients with a very low CI and a low PCWP. As little as 200 ml of Haemaccel was sufficient to raise the cardiac output to normal levels. It is suggested that the high initial cardiac indices reported in many series may be because fluid had been infused before measurements were made. These measurements may not reflect the true haemodynamic state in untreated hypertensive patients.

Another explanation is that there may be a major difference in haemodynamic status between non-proteinuric and proteinuric hypertension in pregnancy. The development of proteinuria may indicate an increase in capillary permeability leading to a marked loss of circulating protein, not only into the urine, but also into the gut and extracellular space. (It is noteworthy that in all of the cases which required caesarean section in the present study there was marked ascites, and in many cases the bowel itself was oedematous.) The loss of circulating albumin into the extracellular space could cause a decrease in total plasma circulating protein, a decrease in plasma and total blood volume, and hence a decrease in central venous and ventricular filling pressures, and a decrease in cardiac output. The increased SVR in these cases might then be at least partially secondary and compensatory to the decrease in cardiac output and circulating blood volume. If this explanation is correct, it could have important implications with regard to management of patients with gestational proteinuric hypertension as it would be important to restore the blood volume and cardiac output before attempting to lower the blood pressure with anti-hypertensive agents. Decreasing the blood pressure without restoring the blood volume would cause a fall in cardiac output and possibly a fall in choriodecidual blood flow which could compromise the fetus. In particular, the decrease in total vascular resistance and expansion in vascular capacity caused by dihydralazine may cause a fall in central venous pressure, a decrease in cardiac output and a decrease in uterine blood flow. This may explain the precipitous fall in blood pressure and occurrence of fetal distress which is sometimes produced by even small doses of dihydralazine, particularly when the drug is given as an intravenous bolus (Vink *et al.* 1980).

The initial PCWP in most of our patients appeared to be abnormally low (mean 5 mmHg, range 0–10). The PCWP in normal patients in late pregnancy has unfortunately not been established. Rose *et al.* (1956) reported a mean of 5·4 mmHg (range 1–9) and Groenendijk *et al.* (1984) reported a mean PCWP of 9 mmHg (range 6–12). The 'control' PCWP measurements reported in patients with severe gestational hypertension vary from 2 to 22 mmHg (Phelan & Yurth 1982; Benedetti *et al.* 1980; Rafferty & Berkowitz 1980; Hankins *et al.* 1984; Henderson *et al.* 1984). Groenendijk *et al.* (1984) reported that a significant proportion of patients with severe untreated gestational proteinuric hypertension had a relatively low initial PCWP, confirming the present findings.

It has been suggested that acute volume expansion in pregnancy hypertension may cause worsening of the condition (Assali & Vaughn 1977). Our findings, however, do not support this view. Infusion of between 200 and 600 ml of Haemaccel over a period of 90 min produced significant increases in CI and SVI, and a definite reduction in SVR but no change in MAP or DBP. Moreover, lower infusion rates of dihydralazine were required to lower the BP to acceptable limits. This finding suggests that volume expansion has a 'partial vasodilatory' effect as proposed by Groenendijk *et al.* (1984). In their study the volume expansion was accomplished over a period of 12–24 h, and the volume required was between 1500 ml and 3500 ml. In our study a maximum of 600 ml of Haemaccel was infused over a period of 90 min. At no time did any of our patients develop any features (clinical or radiological) of incipient pulmonary oedema.

The patients in this study with severe gestational proteinuric hypertension appeared to have underfilling of the circulation with a low cardiac index and this was restored to normal by infusion of a relatively small volume of fluid. The increase in cardiac output following fluid infusion with the associated decrease in vascular resistance may be of considerable therapeutic importance in maintaining or increasing uterine and choriodecidual blood flow before the administration of vasodilatory anti-hypertensive drugs.

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Haemodynamic changes associated with caesarean section under epidural anaesthesia

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Summary. Serial haemodynamic investigations were performed in 15 women delivered by elective caesarean section under epidural anaesthesia at 38–40 weeks gestation. Cardiac output was measured by Doppler and cross-sectional echocardiography at the aortic valve. No haemodynamic changes were demonstrable after attainment of surgical anaesthesia (T5 or above). Stroke volume increased 13% after delivery of the placenta and remained elevated until the end of the operation at which time cardiac output was 11% above pre-operative values. Stroke volume and cardiac output fell during the first postoperative day. Heart rate remained elevated at pre-operative values for 48 h after delivery. There was a fall in heart rate and cardiac output between the second and the sixth days after delivery. By 2 weeks after delivery cardiac output was 28% lower than pre-operative values. Compared with pre-operative values, diastolic blood pressure was lower on the first and second postnatal days.

In recent years the prevalence of caesarean delivery has increased (Chalmers 1985) and an increasing proportion of such deliveries have been conducted under epidural anaesthesia (Moir & Thorburn 1986). The extensive epidural block required for surgical anaesthesia may have profound haemodynamic effects, with hypotension reported in 7–45% of subjects (Hallworth *et al.* 1982; Lewis *et al.* 1983). In contrast to blood pressure, relatively little is known about the changes in cardiac output during and after caesarean section under epidural anaesthesia.

Ueland *et al.* (1972) reported little change in cardiac output, measured by the dye dilution technique, following administration of epidural anaesthesia and a 25% increase in cardiac output after delivery. However, serial investigations were performed on supine subjects in whom caval compression by the gravid uterus reduced cardiac output before delivery (Ueland *et al.* 1972). Subsequent workers using M-mode echocardiography (Maruta 1982) and impedance cardiography (Milsom *et al.* 1985; Ramanathan *et al.* 1986) have reported conflicting results. Following establishment of epidural anaesthesia, cardiac output has been reported to be increased (Milsom *et al.* 1985), decreased (Maruta 1982)

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and unchanged (Ramanathan *et al.* 1986). Milsom *et al.* (1985) suggested that there was a further increase in cardiac output after delivery but Maruta (1982) demonstrated no significant change. Measurements of stroke volume by impedance cardiography have been shown to correlate poorly with those made by thermodilution during caesarean section (Secher *et al.* 1979) and the validity of the assumptions of the technique during pregnancy has been questioned (De Swiet & Talbert 1986). M-mode echocardiography has not been validated in pregnancy and the assumptions of the technique may not be valid during pregnancy (Robson *et al.* 1987*a*). There is a need for a serial study, using accepted methods and avoiding postural artefacts, to investigate the haemodynamic changes associated with caesarean section under epidural anaesthesia.

Cardiac output can be calculated from cross-sectional echocardiographic measurement of aortic orifice area combined with Doppler ultrasound measurement of aortic blood velocity. The technique has been validated in pregnancy (Easterling *et al.* 1987) and allows reproducible non-invasive measurement of cardiac output in pregnant subjects (Robson *et al.* 1987*a*). We have used this method to investigate the serial haemodynamic changes during and after caesarean section performed under epidural anaesthesia.

Subjects and methods

Twenty-six healthy women without evidence of cardiovascular disease admitted for elective caesarean section at 38–39 weeks gestation were recruited from the antenatal ward. The procedure was explained to each subject and informed consent was obtained. The experimental protocol was approved by the ethics committee of Newcastle Health Authority. Five subjects subsequently required ephedrine because of hypotension during epidural anaesthesia. Because of the haemodynamic effects of ephedrine these five subjects were excluded. Serial measurements were obtained in 15 of the remaining subjects and the details of this group are shown in Table 1.

Table 1. Details of subjects in the study

Number	15	
Nulliparous	4	
Age (years)	26	(5)
Height (m)	1·54	(0·06)
Weight (kg)	55	(6)
Gestation at delivery (weeks)	38·8	(0·6)
Birthweight (kg)	3·22	(0·60)

Results are mean (SD) values.

Each subject received oral ranitidine (150 mg) on the evening before and on the morning of the operation together with oral sodium citrate 0·3 M (30 ml) on arrival in theatre. An intravenous infusion of Ringer's lactate solution was established and 500 ml infused rapidly. The infusion was continued at a rate of 500 ml/15 min until the start of the operation and then 500 ml/30 min thereafter. The epidural space was located with a 16-gauge Tuohy needle (L2/3 or L3/4 interspace) and an epidural catheter inserted. A 3-ml test dose of 0·5% bupivacaine was then injected through the catheter. After 5 min, a further 10–20 ml of 0·5% bupivacaine plain was injected slowly with the subject in the right semi-lateral position (time zero). The dose was determined according to the height of the patient. After 10 min the subject was turned to the left semi-lateral position. Sensory block was assessed using the absence of perception of cold sensation to an ethyl chloride spray at 10, 20, 30 and 40 min after the initial dose of bupivacaine. Further doses of 0·5% bupivacaine were given if the sensory block was below T6 at 20 min. A block up to T5 was judged adequate anaesthesia for surgery. All subjects were given oxytocin, 10 units intravenously at the time of delivery of the infant. Four required intravenous opioids after delivery because of pain.

Investigations were performed at the following time points: before anaesthesia; start of the operation; after delivery of the placenta; at the end of the operation; 1 h after the operation and on days 1, 2, 6 and 14 after delivery. All measurements were performed with the subject in the left semi-lateral position. Investigations after delivery were performed in a warm quiet room after the woman had a minimum of 10 min rest.

Aortic velocities were recorded with continuous wave Doppler ultrasound using a 2-MHz transducer (Vingmed) placed in the suprasternal notch. A spectrum analyser (Doptek) performed fast Fourier transform analysis of the Doppler signal and the output was converted to velocity of flow according to the Doppler equation:

$$V = \frac{f \times c}{2f_0 \times \cos\theta}$$

where V = velocity of erythrocytes, f = Doppler frequency shift, c = average speed of propagation of ultrasound in tissue, f_0 = emitting frequency of the transducer, and θ = angle between the ultrasound beam and the direction of blood flow. The direction of the ultrasound beam was adjusted until the highest velocities with the least spectral dispersion were obtained. These velocities were then stored in the computer memory and it was assumed that they represented the velocities at the aortic orifice and that the ultrasound beam was parallel with flow ($\cos\theta = 1$). The computer then calculated heart rate and velocity integral (area under the velocity curve) using 15/16 of the maximum frequency. This eliminated errors in the calculation of velocity integral from inclusion of any high frequency interference. The average of 8–10 consecutive beats was used for each determination.

Aortic orifice diameter was measured using cross-sectional echocardiography. All measurements were made using a 5-MHz mechanical transducer (Ausonics). The aorta was imaged in the parasternal long axis plane and the orifice diameter was measured during systole. The diameters from five consecutive beats were averaged and the cross-sectional area was calculated from:

$$\pi \times (D/2)^2$$

where D = mean aortic orifice diameter. Cardiac output (CO) was then calculated from the formula:

CO (ml/min) = stroke volume (ml) × heart rate (beats/min) where stroke volume = velocity integral (cm) × cross-sectional area (cm^2).

Blood pressure was measured by an oscillometric technique using an automatic sphygmomanometer (Datascope Accutorr 1). Measurements of systolic, diastolic and mean arterial pressure (MAP) were obtained every minute during echocardiographic investigations, and the mean of three consecutive measurements was used for analysis. Total peripheral vascular resistance (TPVR) was estimated from the formula:

TPVR (dyne .s^{-1}. cm^{-5}) = MAP (mmHg) × 80 ÷ CO (l/min).

Statistical methods

A repeated measures analysis of variance was performed for each variable using the statistical package BMDP. The total variance consists of a component due to differences between subjects (σ_S^2) and a component due to differences within subjects (σ_W^2). The within-subject variance comprises a component due to differences between time points (σ_T^2) and a component representing the residual variability (σ_R^2). Due to the problem of multiple significance testing, the differences between time points were compared using the studentized range at the 1% level (range = $q_{(V)} \times [\sigma_R \div \sqrt{n}]$, where $q_{(V)}$ = critical value for comparing two time points, σ_R^2 = residual mean square with v degrees of freedom and n = number of subjects. Thus any difference greater than the studentized range was considered statistically significant.

Results

Serial measurements were obtained from 15 subjects all of whom had an uncomplicated caesarean section (mean estimated blood loss 625 ml, SD 200 ml). The mean total dose of 0·5% bupivacaine administered was 21 (SD 3) ml, and the mean volume of Ringer's lactate infused before the start of the operation was 1·9 (SD 0·2) litres. The haemodynamic results are shown in Table 2.

Systolic blood pressure showed no significant changes during the period of study. Diastolic blood pressure was significantly lower than pre-operative values at 24 and 48 h after delivery. Heart rate remained relatively stable during the operation and for the first 48 h after delivery and thereafter fell. By 2 weeks postoperatively heart rate was 19% lower than pre-operative values. Velocity integral increased after delivery of the placenta and remained elevated until the end of the operation, falling thereafter till 1 day after delivery. Aortic area fell after delivery, the difference being statistically significant by 1 day with a further significant fall between postpartum days 1 and 14. Stroke volume remained stable after establishment of the epidural block and then increased after delivery of the placenta. Values remained elevated during the operation and then fell between the end of the operation

Table 2. Haemodynamic changes during and after epidural caesarean section

	Before caesarean section	During caesarean section			After caesarean section						
		Start	Del plac.	End	1 h	1 day	2 days	6 days	14 days	SEM	SR
Systolic BP (mmHg)	113	107	113	106	111	109	107	111	113	2	8
Diastolic BP (mmHg)	68	65	67	65	66	63	61	64	63	1	5
Heart rate (beats/min)	85	84	81	84	78	84	84	75	69	2	9
Velocity integral (cm)	20·1	20·5	22·8	22·9	21·0	19·4	19·2	19·3	19·4	0·4	1·4
Aortic area (cm²)	4·17	4·09	4·15	4·09	4·07	4·01	3·96	3·90	3·84	0·03	0·12
Stroke volume (ml)	84	84	95	94	85	78	76	75	75	2	6
Cardiac output (l/min)	7·14	7·08	7·69	7·90	6·65	6·44	6·32	5·60	5·11	0·19	0·70
Total peripheral vascular resistance ($cm^{-5}.s^{-1}$.dyn)	937	920	879	829	1022	978	958	1146	1243	37	139

Del plac., After delivery of the placenta; BP, blood pressure; SEM, standard error of mean determined from analysis of variance; SR, studentized range

and 1 h after delivery. There was a further fall between 1 h and 24 h and thereafter no further change. By 2 weeks postpartum stroke volume was 11% lower than pre-operative values. No change in cardiac output was demonstrated at the start of the operation but there was an 11% increase, relative to pre-operative values, by the end. One hour after delivery cardiac output had fallen relative to values obtained at the end of the operation and there was a further fall between postpartum days 2 and 6. By 2 weeks after delivery cardiac output was 28% lower than pre-operative values. No change in total peripheral vascular resistance was demonstrated during the operation. One hour postoperatively there was an increase relative to values obtained during the operation. A further increase occurred between postpartum days 2 and 6 such that vascular resistance was significantly greater than pre-operative values by the sixth post-operative day.

Discussion

The methods used in this study have been validated against the Fick technique by the authors (Robson *et al.* 1987*a*), and cardiac output measured by the Doppler method correlates closely with thermodilution measurements during pregnancy (Easterling *et al.* 1987). The within-subject intra-observer and temporal coefficients of variation of the technique are less than 5% (Robson *et al.* 1987*a*) suggesting that the method is suitable for studying serial changes in pregnant women.

James *et al.* (1984) were the first to measure cardiac output in pregnancy using the Doppler technique. They studied women who were delivered by caesarean section under epidural and general anaesthesia before and up to 24 h after delivery. Our results confirm their findings of an increase in cardiac output 15–30 min after delivery and a return to pre-operative values by 1 h. However, they reported no change in stroke volume during the operation. This is in disagreement with the present results and those of previous studies (Ueland *et al.* 1972; Maruta 1982; Milsom *et al.* 1985), and may be partly explained by the different methods of measuring aortic diameter. James *et al.* (1984) used A-mode rather than cross-sectional echocardiography. The latter method is preferable because the diameter can always be measured perpendicular to the long axis of the aorta and a fixed site is easier to define (Skjaerpe *et al.* 1985). Furthermore stroke volumes calculated using diameters obtained by cross-sectional echocardiography correlate the closest with stroke volumes determined by thermodilution (Gardin *et al.* 1985).

The values obtained for pre-operative cardiac output are comparable to those reported previously by us at 38 weeks gestation using the same method (Robson *et al.* 1987*b*) and are within the range reported by other workers using other techniques in the left lateral position during late pregnancy (Vorys *et al.* 1961; Kjeldsen 1979). Compared with pre-operative values, no difference in cardiac output was demonstrated after attainment of surgical anaesthesia. This finding is in agreement with a number of previous studies (Stenger *et al.* 1965; Ueland *et al.* 1972; Ramanathan *et al.* 1986). Two groups, however, have reported significant changes in cardiac output during this period. Maruta (1982) demonstrated a fall in stroke volume and cardiac output following epidural anaesthesia. This may be related to the lower volume of Ringer's lactate infused by Maruta (<1 litre). Increasing the volume of 'pre-load' to 2 litres has been reported to reduce the incidence of hypotension (Lewis *et al.* 1983). Milsom *et al.* (1985) reported an increase in heart rate and cardiac output after attainment of surgical anaesthesia. This may have been partly due to the intravenous administration of atropine sulphate (0·5 mg) before the epidural.

After delivery of the placenta, stroke volume was found to increase while heart rate remained unchanged. Similar findings have been reported previously (Ueland *et al.* 1972; Maruta 1982; Milsom *et al.* 1985). The increase in stroke volume may reflect augmentation of venous return secondary to a shift of blood from the choriodecidual space into the central circulation as the uterus contracts down after delivery. The reported increase in central venous pressure immediately after delivery is consistent with this suggestion (Ueland *et al.* 1972).

Cardiac output fell during the first postoperative day due primarily to a decrease in stroke volume. This is in contrast to the haemodynamic changes after vaginal delivery when cardiac output appears to be maintained at prelabour values for up to 48 h (Robson *et al.* 1987*c*). This may reflect the increased blood loss associated with operative delivery. Maternal blood volume has been reported to be 7–19% lower 1–10 h after caesarean section than after vaginal delivery (Pritchard 1965; Ueland 1976). Thus the reduced stroke volume may reflect a reduction in venous return secondary to the fall in circulating blood volume. We have observed a similar pattern of change in women experiencing primary postpartum haemorrhage (unpublished observations). No further fall in stroke volume was demonstrated after the first day. Corresponding studies of blood volume have reported no reduction in blood volume during the first week after caesarean delivery (Pritchard 1965; Ueland 1976). By 2 weeks after delivery cardiac output was 28% lower than pre-operative values. This is slightly greater than the decrease reported by Maruta (1982) at 1–2 weeks after caesarean section but is in close agreement with our previous postnatal study (Robson *et al.* 1987*b*).

Thus caesarean section under epidural anaesthesia appears to result in relatively small changes in maternal haemodynamics. Apart from an earlier reduction in cardiac output in subjects delivered by caesarean section, postnatal changes appear to be comparable to those encountered after vaginal delivery. During establishment of epidural anaesthesia, five subjects required ephedrine to correct hypotension. Marked changes in cardiac output were encountered in this group. As this study was designed to investigate haemodynamic changes during caesarean section after establishment of anaesthesia it was felt reasonable to exclude them. Little is known about the changes in cardiac output during establishment of epidural anaesthesia and further study is needed. Doppler echocardiography is particularly suitable for the serial measurement of cardiac function, and its potential for studying haemodynamics during caesarean section in normal and complicated pregnancies is considerable.

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Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population

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Summary. Previous studies have suggested that increased dietary calcium is associated with a decreased occurrence of pregnancy-induced hypertension. In this study 106 young healthy nulliparous women, residing in Quito, Ecuador, were enrolled in a double-blind, randomized, controlled clinical trial. From 24 weeks gestation until delivery they received either 2 g of elemental calcium per day or a placebo. Calcium supplementation was associated with a significantly decreased risk of pregnancy-induced hypertension, with 4·1% developing pregnancy-induced hypertension in the treatment group versus 27·9% in the placebo group. Treatment was associated with a decrease in both systolic and diastolic blood pressure over the course of pregnancy. In addition, there was a small but significant increase in serum ionized calcium levels in the calcium-supplemented group during the treatment period.

Epidemiological studies have suggested a negative association between levels of dietary calcium intake and the incidence of pregnancy-induced hypertension (PIH) in diverse populations (Belizan & Villar 1980; Villar *et al.* 1983). Furthermore, it has been suggested that dietary calcium intake of at least 2 g/day during pregnancy is necessary to maintain a positive calcium balance (Duggin *et al.* 1974). In addition, previous clinical trials have indicated that the use of supplemental dietary calcium is correlated with a significant decrease in blood pressure in normotensives (Belizan *et al.* 1983*a*), essential hypertensives (Grobbee & Hoffman 1986), and in normotensive pregnant women (Belizan *et al.* 1983*b*). Furthermore, the results of some recent clinical trials have suggested that daily calcium supplementation may be associated with a decreased risk of PIH (Kawasaki *et al.* 1985; Villar *et al.* 1987), although this association has not been demonstrated by others (Marya *et al.* 1987).

The purpose of this study was to investigate the effect of daily 2 g calcium supplements on lowering the risk of PIH, in an Andean population with a reported high frequency of PIH (López-Jaramillo *et al.* 1984; Jijón 1985) and to assess the relation between calcium intake from supplements and serum ionized calcium levels and blood pressure.

Subjects and methods

The study was a prospective, randomized, double-blind, controlled clinical trial. Women

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attending the antenatal outpatient clinics in the Hospital Gineco-Obstétrico Isidro Ayora in Quito, Ecuador, during a 30-month period between 1984 and 1986 were asked to participate. Subject selection criteria included: nulliparity, age ≤25 years, certainty about the date of the last menstrual period, registration at the clinic for the first prenatal visit before 24 weeks gestation, and residency in Quito (2800 m altitude) for a period of at least 1 year before conception. Furthermore, the selection criteria required that at the time of the first prenatal visit, prospective subjects have a combined systolic/diastolic blood pressure of <120/80 mmHg and be free of any underlying medical disorders, based on a comprehensive medical examination and routine laboratory tests. Patients were excluded if they had a history of cardiovascular, renal, or endocrinological disease, or if they were taking any type of drug or vitamin/mineral preparation.

A total of 106 women satisfactorily met the subject selection criteria. Using a table of random numbers each patient was assigned independently in sequence to one of two treatment regimens. Treatment assignment was double blind, with the composition of the tablets unknown to the patients and to all clinical personnel involved in the study. The calcium-supplemented group received four tablets daily, each tablet containing 500 mg elemental calcium (gluconate). Thus, each woman in the supplemented group received a total of 2000 mg elemental calcium daily, beginning after 23 weeks gestation and continuing until delivery. The placebo group also received four tablets daily of the same size, weight, colour and organoleptic characteristics as the calcium tablets. The containers and the tablets for both groups were prepared in the Facultad de Quimica y Farmacia, Universidad Central del Ecuador. All patients received prenatal care according to the normal protocol followed in the Hospital Gineco Obstétrico Isidro Ayora. The study protocol was approved by the Instituto de Investigaciones, Facultad de Ciencias Médicas.

Blood pressure, weight and height were measured at the initial prenatal visit. Subsequently only blood pressure and weight were taken at every prenatal visit (28, 32, 36, 38 and 40 weeks gestation) and at ≥48 h after delivery. Immediately before blood pressure measurement, each patient rested in an upright position for 10 min. Blood pressure was measured twice from the right arm while in the seated position, with a between-measurement interval of 2 min. All blood pressures were measured by the same investigator (M.N.) with a mercury sphygomanometer (Nova-Presameter, Riester, Germany), which was calibrated by the Instituto Ecuatoriano de Normalización y Medidas, Quito. The systolic blood pressure was recorded with the appearance of the first Korotkoff phase, and the diastolic blood pressure with the disappearance of the fifth Korotkoff sounds. The mean of the two recorded blood pressures was used for the statistical analysis. At each prenatal visit and at the first postpartum visit, blood samples were obtained from each subject, who had fasted overnight, for the purpose of measuring serum ionized calcium values. All samples were obtained between 08.00 and 10.00 hours. Each sample was analysed twice under anaerobic conditions within 4 h of collection by the electrode selective ion method (Nova Biomedical, Massachusetts, USA). The variation of the two samples analysed was less than 1%. The mean of the two measures was used for the statistical analysis. In addition, the patient's first urine sample of the morning was tested for protein.

The diagnosis of PIH was defined by a blood pressure of ≥140/90 mmHg or a rise of 30 mmHg in systolic or 15 mmHg in diastolic blood pressures from the baseline values observed at 24 weeks, on at least two occasions ≥6 h apart. Patient compliance with the treatment protocol was assessed during each prenatal visit by counting the number of tablets remaining in the container and by random unscheduled home visits by the investigators. A total of 106 women completed the study: 55 in the calcium-supplemented group and 51 in the placebo group.

Statistical methods

Differences between the supplemented and placebo groups in the occurrence of PIH were analysed statistically using a 2 × 2 contingency table analysis, with calculation of the χ^2 statistic, using Yates' correction. Repeated measures analysis of covariance (ANCOVA) was the statistical method used to examine treatment group differences in systolic and diastolic blood pressure and serum ionized calcium over the course of gestation. The repeated measures were the values obtained at weeks 28, 32, 36 and 38. The covariate in each analysis was the pretreatment level of the outcome variable examined (i.e. the value obtained at week 24); it was included in the analysis as a precaution against imperfect randomization in treatment group assignment. Two-sample *t*-tests were also conducted to determine the extent of pretreatment group differences, as well as differences at the postpartum measurement. Postpartum data were analysed separately from predelivery measures because processes operating before and after delivery are not necessarily similar. In all statistical analyses an alpha level of 0·05 was utilized.

Only women with no missing values for any of the covariate and outcome variables were included in these statistical analyses, 49 in the calcium-supplemented group and 43 in the placebo group. Six women in the calcium-supplemented group and eight in the placebo group were eliminated from analysis because they were delivered before 38 weeks, although none was delivered before 36 weeks and none had any signs of PIH.

Previous studies led to an expectation of a 25% rate of PIH in a non-supplemented population with the selection criteria employed (Bucheli *et al.* 1982; Jijón 1985). With the sample size obtained, employing a one-tailed alpha of 0·05 and a minimum power of 0·8, this sets a requirement that PIH risk be reduced to approximately ≤7·5% in the treatment group (i.e. a 70% attributable risk percentage for PIH due to exposure to the non-supplementation condition) to achieve statistical significance (Cohen 1977).

Results

Demographic characteristics of subjects in the study are listed in Table 1. Women in both treatment groups were similar in age, height, marital status and educational level. None of the pregnancies was associated with preterm delivery (before 36 weeks gestation), low birthweight (<2500 g) or perinatal mortality. The average weekly weight gain (g/week) in the placebo group was slightly higher than in the supplemented group (452·1, SEM 27·8 *vs* 412·1, SEM 25·5). The birthweight in the calcium-supplemented group was slightly higher than in the placebo group (3097, SEM 39·8 g *vs* 2832, SEM 49·6 g). This difference was not statistically significant. The average length of gestation was significantly longer (*t*-test: $P<0·05$) in the calcium-supplemented group (39·3, SEM 0·08 weeks, $n=55$) than in the placebo group (38·7, SEM 0·07 weeks, $n=51$).

The overall frequency of PIH in this sample was 15·2% ($n=14$). Calcium supplementation was associated with a significantly decreased risk of PIH (risk reduction=23·8%; 95% CI 7·1% to 40·4%; $P=0·004$), with 4·1% ($n=2$) developing PIH in the treatment group *vs* 27·9% ($n=12$) in the placebo group.

The pattern of serum ionized calcium levels from weeks 24 to 38 and in the postpartum

Table 1. Characteristics of the women in the two treatment groups

Maternal characteristics	Placebo group ($n=43$)	Calcium group ($n=49$)
Age (years)	18·2 (2·2)	18·7 (2·7)
Height (cm)	152·9 (6·5)	151·3 (4·9)
Marital status (%)		
Single	5·9	3·6
Married	86·3	87·3
Common law	7·8	9·1
Educational level (%)		
Incomplete elementary school	9·8	14·6
Completed elementary school	15·7	9·1
Incomplete high school	41·2	34·5
Completed high school	19·6	25·4
Others	13·7	16·4
Weight gain (g/week)	452·1 (180·0)	412·1 (176·4)
Birthweight (g)	2832 (318)	3097 (276)

Results are mean (SD) values.

period in both treatment groups is shown in Table 2 and Fig. 1. The mean serum ionized calcium level at the pretreatment assessment (week 24) was slightly higher in the placebo group than in the supplemented group, but this difference was marginally not statistically significant at the standard 0·05 alpha level (*P*=0·07). After adjusting for pretreatment group differences, the average serum ionized calcium level over the repeated post-treatment measurements was significantly higher in the supplemented than in the placebo groups [ANCOVA: treatment effect: F(1,89)=84·30; *P*<0·001]. By week 28, serum ionized calcium level in the supplemented group was noticeably higher than in the placebo group, and remained higher through the remainder of pregnancy. The week-by-week pattern in serum ionized calcium was marginally significantly different in the two groups [ANCOVA: group × time interaction effect: F(3,270)=2·76; *P*=0·04]. However, there were no group differences in time-related linear trends apparent over the course of the post-treatment period. The analysis of postpartum serum ionized calcium levels indicated no significant treatment group differences.

The pattern of systolic blood pressure from weeks 24 to 38 and in the postpartum period in both treatment groups is shown in Table 3 and Fig. 2. The mean systolic blood pressure level at the pretreatment assessment was slightly higher in the placebo group than in the supplemented group, but this difference was not statistically significant (*P*=0·13). After adjusting for pretreatment group differences, the average systolic blood pressure level over the repeated post-treatment measurements was significantly lower in the supplemented than in the placebo groups [ANCOVA: treatment effect: F(1,89) = 21·73; *P*<0·001]. The general pattern in both treatment groups was an increase in systolic blood pressure over the course of pregnancy [ANCOVA: time effect: F(3,270) = 31·01; *P*<0·001]. However, the week-by-week pattern in systolic blood pressure was significantly different between the two groups [ANCOVA: group × time interaction: F(3,270)=3·70; *P*=0·01], with a general pattern indicating a higher rate of increase in the placebo group than in the supplemented group (see Table 3: differences in adjusted means). The placebo group also had a significantly higher systolic blood pressure (*P*=0·02) at postpartum measurement.

The pattern of diastolic blood pressure from weeks 24 to 38 and in the postpartum period in both treatment groups is shown in Table 4 and Fig. 3. The mean diastolic blood pressure at the pretreatment assessment was slightly higher in the placebo group than in the supplement group, but this difference was marginally not statistically significant (*P*=0·07). After adjusting for pretreatment group differences, the average diastolic blood pressure level over the repeated post-treatment measurements was significantly lower in the supplemented than in the placebo groups [ANCOVA: treatment effect: F(1,89)=6·10; *P*=0·015]. Over the course of the post-treatment measures, there was a general pattern for both treatment groups showing an increase in diastolic blood pressure [ANCOVA: time effect: F(3,270)=68·52; *P*<0·001]. The week-by-week variation in diastolic blood pres-

Table 2. Serum ionized calcium concentrations (mmol/l) by treatment group

	Placebo group (*n*=43)			Calcium group (*n*=49)			
Gestational age (weeks)	Mean	SEM	Adj. mean	Mean	SEM	Adj. mean	Diff. adj. mean
24	1·15	0·006		1·13	0·004		
28	1·13	0·006	1·13	1·17	0·004	1·17	0·04
32	1·12	0·006	1·12	1·17	0·003	1·17	0·05
36	1·14	0·005	1·14	1·17	0·004	1·17	0·03
38	1·14	0·005	1·14	1·18	0·004	1·18	0·04
Postpartum	1·18	0·005		1·18	0·004		

SEM, Standard error of the mean; Adj. mean, mean of post-treatment measures during pregnancy, adjusted for pretreatment (week 24) values; Diff adj. mean, difference in adjusted means between treatment groups at week indicated.

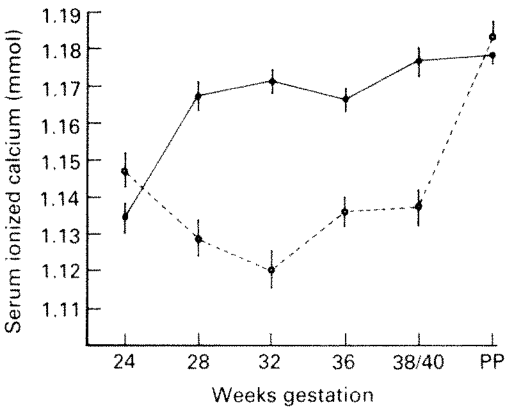

Fig. 1. Variations of serum ionized calcium in the calcium-treated and placebo-treated groups during pregnancy and in the postpartum period (mean ±SEM). ●——●, Calcium (n=49); ○ – – – ○, placebo (n=43). PP, Postpartum.

sure was significantly different in the two groups [ANCOVA: group × time interaction: F(3,270) = 4·59; P=0·004], with a general pattern indicating a higher rate of increase in the placebo group than in the supplemented group (see Table 4: differences in adjusted means). However, at the postpartum measurement there were no significant differences in diastolic blood pressure.

There were no significant differences between the women who developed PIH and those who did not, except for the average weekly weight gain. The women with PIH gained an average of 559·2 g/week (SEM 47·5) whereas the normotensive group gained an average of only 421·4 g/week (SEM 19·8). The mean systolic blood pressure at 24 weeks for women who later developed PIH was 109·7 mmHg (SEM 2·6) and the mean diastolic blood pressure was 69·1 mmHg (SEM 2·0). No woman in this group had proteinuria of >30 mg/dl at the beginning of the study, but by the end of pregnancy (weeks 38/40) their mean blood pressure was 140·3 mmHg (SEM 2·3) systolic and 102·5 mmHg (SEM 2·2) diastolic and all of them had proteinuria >30 mg/dl.

Table 5 shows that the 14 women who developed PIH (12 in the placebo group and two in the supplemented group) had lower serum ionized calcium concentrations throughout the pregnancy compared with the 47 women in the supplemented group who remained normotensive, but similar calcium concentrations when compared with the 37 women in the placebo group who remained normal.

None of the women had any side-effects which could be attributed to the treatments.

Discussion

A high incidence of PIH in the Andean region of Ecuador has been reported (López-Jaramillo *et al.* 1984; Jijón 1985). In addition, a preliminary study at our Hospital Gineco-Obstétrico Isidro Ayora research site (López-Jaramillo 1988) has indicated that dietary calcium intake in prenatal patients is low, with a mean intake of 292 mg/day (SD 126) during the third trimester of pregnancy.

Previous epidemiological studies have suggested a strong correlation between low dietary calcium intake and increased occurrence of PIH (Belizan & Villar 1980; Villar *et al.* 1983). Thus, if the dietary calcium hypothesis is correct, it would appear that pregnant Ecuadorian women may be at increased risk for the develop-

Table 3. Systolic blood pressure (mmHg) by treatment group

	Placebo group (n=43)			Calcium group (n=49)			
Gestational age (weeks)	Mean	SEM	Adj. mean	Mean	SEM	Adj. mean	Diff. adj. mean
24	106·4	1·7		103·2	1·3		
28	107·7	1·6	106·8	101·9	1·1	102·7	−4·1
32	108·9	1·5	108·0	103·4	1·3	104·1	−3·9
36	112·3	1·7	111·4	105·1	1·2	105·9	−5·5
38	120·5	2·4	119·6	108·6	1·3	109·3	−10·3
Postpartum	113·6	1·3		109·4	1·1		

For abbreviations see Table 2.

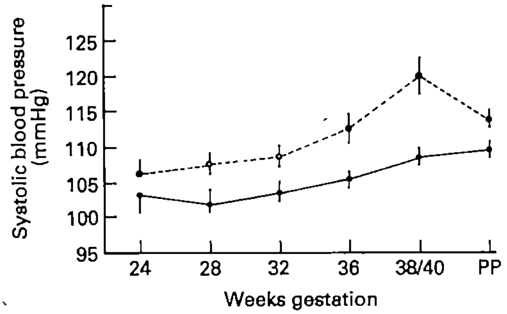

Fig. 2. Variations of systolic blood pressure in the calcium-treated and placebo-treated groups during pregnancy and in the postpartum period (mean ± SEM). ●——●, Calcium (n=49); ○ – – – ○ placebo (n=43) PP, Postpartum.

ment of PIH due to deficient dietary calcium intake.

Our results agree with those reported by Villar *et al.* (1987) and Belizan *et al.* (1983*b*), who found a dose-response relation between calcium supplementation with 1, 1·5 and 2 g/day and blood pressure in late pregnancy. However, the observed beneficial effect of 2 g calcium supplementation on blood pressure and risk of PIH in our study appears more robust. These differences may be due to the younger maternal age (mean 18·2 years) and nulliparity in our sample, lower calcium intake from dietary sources in our population, the effects of Quito's higher altitude (Moore *et al.* 1982), or the fact that Ecuadorian women may constitute a higher risk group for PIH. In contrast, our results differ from Kawasaki *et al.* (1985) who reported a lower frequency of PIH in the calcium-supplemented group (4·5% *vs* 21·2 in the non-supplemented group) but the difference was not statistically significant. This discrepancy may be accounted for by the magnitude of the difference in the amount of calcium supplied (2000 mg *vs* 156 mg) as well as by other methodological differences, i.e. the failure to use a placebo, sample size discrepancies, and the lack of a balanced design in Kawasaki's study. Our results also differ in one respect from a recent randomized, controlled clinical trial by Marya *et al.* (1987) who gave mixed-parity subjects a combination daily supplement of 375 mg calcium and 1200 iu vitamin D. Although there was a significant reduction in both systolic and diastolic blood pressure ($P<0·001$) in the supplemented group during 32 and 36 weeks gestation, the frequency of PIH did not differ significantly between the two groups. It is possible that the relatively low dose of supplement calcium (375 mg/day) in this trial may be responsible for the results.

There is a lack of consensus in the literature concerning the behaviour of serum ionized calcium during pregnancy (Pitkin & Gebhardt 1977; Tan *et al.* 1972; Fogh-Andersen & Schultz-Larsen 1981). The results of the present study show that serum ionized calcium levels increased from weeks 24 to 28 after calcium supplementation was begun. Thereafter, the concentration of serum ionized calcium was maintained constant throughout the remainder of pregnancy at levels which were similar to those observed postpartum. In contrast, the placebo group exhibited a decrease in serum ionized calcium concentration during the same period. These values were significantly lower than those observed in the postpartum period. These results suggest that the behaviour of serum ionized calcium

Table 4. Diastolic blood pressure (mmHg) by treatment group

	Placebo group (n=43)			Calcium group (n=49)			
Gestational age (weeks)	Mean	SEM	Adj. mean	Mean	SEM	Adj. mean	Diff. adj. mean
24	65·9	1·2		63·1	1·0		
28	64·2	1·3	63·2	61·6	1·0	62·5	−0·7
32	67·2	1·6	66·2	62·4	1·0	63·3	−2·9
36	72·1	1·7	71·1	67·1	1·1	68·0	−3·1
38	80·0	2·5	75·0	70·6	1·3	71·5	−7·5
Postpartum	71·0	1·3		69·5	0·9		

For abbreviations see Table 2.

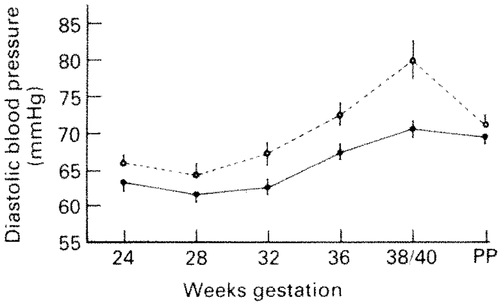

Fig. 3. Variations of diastolic blood pressure in the calcium-treated and placebo-treated groups during pregnancy and in the postpartum period (mean ± SEM). ●——●, Calcium (*n*=49); ○- - -○, placebo (*n*=43). PP, Postpartum.

during pregnancy could be related to the ingestion of dietary calcium.

It has been shown that a significant number of patients with essential hypertension have lower serum ionized calcium levels compared with normotensives (McCarron 1982). In the present study, all women who developed PIH in either group had serum ionized calcium levels significantly lower than the women who remained normotensive in the supplemented group, but similar levels to those who remained normotensive in the placebo group. Moreover, the two women in the calcium-supplemented group who developed PIH did not show an increase in ionized calcium, though they faithfully took 2 g of calcium per day, whereas the other 47 who remained normotensive did show an increase. Experimental data in spontaneously hypertensive rats showed a fall in serum ionized calcium and it has been suggested that this may be due to a defect in intestinal absorption of calcium (McCarron *et al.* 1985; Lucas *et al.* 1986). Unfortunately this present study did not include urinary and faecal calcium levels. On the other hand, the fact that all women in the placebo group had a low serum ionized calcium concentration, but only 27·9% developed PIH, contradicts the simple concept that there is a direct correlation between the serum ionized calcium concentration and PIH. This emphasizes the fact that more studies are needed to clarify the relation between calcium intake and PIH.

On the other hand, an earlier study showed an interrelation between extracellular calcium concentration and vascular synthesis of prostacyclin (PGI_2), a potent vasodilator (López-Jaramillo *et al.* 1987*a*). We have suggested previously that calcium intake may affect the synthesis of PGI_2 (López-Jaramillo *et al.* 1987*b*). This substance is reported to be decreased in the presence of PIH (Makila *et al.* 1984). However, several other hypotheses have been proposed to explain the mechanism by which calcium supplementation acts to reduce blood pressure although none has been substantiated consistently (McCarron 1985; Lau *et al.* 1984). Regardless of the mechanism, the results of our study suggest that calcium supplementation during the third trimester is a safe, effective, and cost-effective preventive measure which can significantly reduce the risk of PIH.

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Dr Margaret Weigel of the University of Illinois at Urbana-Champaign provided constructive criticism of the manuscript.

Table 5. Serumionized calcium concentration (mmol/l) by treatment group and by presentation of pregnancy-induced hypertension (PIH)

Gestational age (weeks)	Placebo group (*n*=43)		Calcium group (*n*=49)	
	Normal (*n*=31)	PIH (*n*=12)	Normal (*n*=47)	PIH (*n*=2)
24	1·14 (0·007)	1·15 (0·009)	1·13 (0·004)	1·15 (0·01)
28	1·13 (0·005)	1·12 (0·006)	1·17 (0·004)	1·13 (0·03)
32	1·12 (0·007)	1·11 (0·006)	1·17 (0·002)	1·13 (0·01)
36	1·13 (0·005)	1·13 (0·009)	1·17 (0·002)	1·10 (0·03)
38	1·13 (0·005)	1·14 (0·009)	1·18 (0·004)	1·15 (0·01)
Postpartum	1·18 (0·005)	1·17 (0·006)	1·18 (0·004)	1·18 (0·01)

Results are mean (SEM) values.

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Midwifery in the Netherlands. The Wormerveer study; selection, mode of delivery, perinatal mortality and infant morbidity

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Summary. Between 1969 and 1983 a group of 7980 pregnant women, booked consecutively at a practice of freestanding midwives in Wormerveer, the Netherlands, was studied. They gave birth to 8055 children. Perinatal mortality in the total group was low (11·1 per 1000) compared with national figures of 14·5 per 1000 between 1969 and 1983. The highest mortality (51·7 per 1000) was found in the group of 1430 infants born after maternal referral during pregnancy to a specialist obstetrician. The perinatal mortality in the group selected during pregnancy as low-risk cases was very low (2·3 per 1000). The caesarean section rate in the total group was 1·4% and 0·4% in the selected low-risk group. Of the 5985 infants born alive under sole care of a midwife, 3·8% were admitted to hospital. Emergency admission because of birth asphyxia occurred in 0·4%. Convulsions within 48 h of birth at term occurred in seven (0·9 per 1000) in the total group and in five infants born in the selected group (0·8 per 1000). Selection of pregnant women into groups with high and with low risk is possible with the relatively modest means available to the midwife.

In the Netherlands a woman with an uncomplicated pregnancy and an uncomplicated obstetric and medical history can choose between a home delivery or a hospital delivery. Prenatal, intrapartum and postnatal care are provided by her midwife or sometimes by her general practitioner. Midwives are fully qualified and licensed to provide independent care during normal pregnancy and childbirth. The midwife or general practitioner is expected to refer the pregnant woman to a specialist obstetrician in a hospital in cases of medical or obstetric pathology, according to an officially approved list of medical and obstetric complications devised by Kloosterman (Keirse 1982; Kloosterman 1984). The Dutch government supports this organization by providing for and supervising the training of midwives in special schools, and by protecting them economically. In those districts of the country where one or more midwives are practising, the midwife and not the general practitioner is paid by the compulsory health insurance of the Health Service for normal obstetric care. Specialist care during pregnancy and at delivery

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is remunerated only if medical reasons or obstetric pathology warrant such care. The Dutch government, moreover, supports financially the 'Maternity Home Help Organization', a nationwide organization which places well-trained maternity-aid-nurses at the disposal of young mothers. These maternity-aid-nurses assist the midwife or general practitioner during the delivery. They take care of the mother and her child and perform household duties during the first 8 days after delivery.

In 1985, 179 190 babies were born in the Netherlands: 61·2% in a hospital, 36·6% at home, 1·3% in a midwife school and 0·6% in a maternity home. The remaining 0·3% were babies born abroad to women normally resident in the Netherlands (Netherlands CBS 1987). A maternity home help (MHH) nurse assisted at 60 642 (92·6%) of the 65 518 home births. In the MHH group, 47 stillbirths were registered; 20 newborns died at home and 48 babies died after referral to a hospital during the first week of life. The perinatal mortality of 60 642 home births was 1·9 per 1000; in the same year the perinatal mortality in the Netherlands was 9·8 per 1000. Of the 60 595 livebirths at home, 1765 infants (2·9%) were admitted to a hospital during the first 7 days of life. Little is known about the indications for hospital admittance. To investigate the procedures used for selecting maternity care, and their results, the Department of Obstetrics and Gynaecology of the University of Amsterdam studied (prospectively) a group of pregnant women who booked at a practice of freestanding midwives in a suburban area north of Amsterdam.

Subjects and methods

In the period October 1969 up to and including March 1983, 8480 women were booked for delivery either at home, or in the small maternity unit at Wormerveer, or in hospital but under the supervision of a midwife. The most recent deliveries in this sample took place in October 1983. The catchment area of the maternity home comprises about 40 000 inhabitants. Only women with an uncomplicated medical and obstetric history book at the practice of freestanding midwives. Women with medical or gynaecological disorders, or those who have experienced serious complications during previous pregnancies, are referred to the specialist obstetrician during the first trimester of pregnancy. During the study period about 80% of all women referred came to one regional hospital. Medical disorders were the reason for the referral in 188 women, 71 were nulliparous and 117 were parous. Previous treatment for infertility was the reason for specialist care in 162 women (3·7% of all nulliparous women). In 110 women (52 nulliparous and 58 parous), a gynaecological abnormality was the reason for referral. In 663 women the reason for referral to a specialist obstetrician was the obstetric history (13·2% of all parous women).

We estimate that 92% of all nulliparous women in the catchment area and 79% of all parous women booked at the midwives' practice. Thus 8480 women residents of Wormerveer and its immediate vicinity booked at the midwives' practice. Of these women 11 were found not to be pregnant (0·1%), in 181 (2·1%) the pregnancy miscarried before 16 completed weeks gestation, two women (0·02%) had an ectopic pregnancy, and 112 women (1·3%) moved to another city during pregnancy.

Overall, 183 pregnant women (2·2%) were referred to the obstetrician before 20 weeks gestation. Nine women gave birth to a fetus weighing less than 500 g and two women were delivered of a hydatidiform mole after 20 weeks.

The remaining 7980 women are the subject of this study.

The group consisted of 4000 nullipara (50·1%) and 3980 (49·9%) parous women. The women gave birth to 8055 children, including 75 sets of twins.

During the first years of the study a minority of the deliveries were attended by general practitioners. During most of the time of the study (up to 31 December 1982) a high proportion of the deliveries attended by midwives took place in a small maternity unit located at Wormerveer, in the centre of the area. The women could also choose home delivery. For specialist care the women had to be referred to one of the regional hospitals. During the last months of the study (after 31 December 1982) the maternity home was closed for economic reasons and the women under the care of the midwives could choose between a home delivery and a hospital delivery. The results of the selection system were judged from the relation between perinatal mortality and morbidity and the place of delivery: either at home, in the maternity unit and (sometimes) in a hospital under supervision of a midwife, or in a hospital under supervision of a specialist

Table 1. Place of birth of the 8055 infants born in the study group of 7980 women and perinatal mortality (stillbirth and early neonatal mortality)

Place of birth	Women *n* (%)	Infants *n* (%)	Perinatal mortality *n* (per 1000)	
Hospital after maternal referral				
During pregnancy	1367 (17·1)	1430 (17·7)	74 (51·7)	
During delivery	632 (8·0)	637 (7·9)	7 (11·0)	(2·3)
At home and in maternity unit	5981 (74·9)	5988 (74·3)	8 (1·3)	
Total	7980 (100)	8055 (100)	89 (11·1)	

obstetrician. The latter group was subdivided into two categories: women referred to the obstetrician because of complications during pregnancy, and women referred to the obstetrician during labour or delivery. Women who were not referred during pregnancy, and who therefore started labour under the care of the midwife, are designated as the 'selected group', i.e. the low-risk group selected for labour and delivery under care of the midwife.

The midwives kept written records of care during pregnancy, labour and delivery, and the postnatal period. All these reports were collected, as were the reports from specialist obstetricians and paediatricians on the patients treated by them. All women and infants were traced after referral, and all perinatal deaths, instrumental and operative deliveries were recorded. Perinatal death was classified according to Cole *et al.* (1986) and Hey *et al.* (1986).

Infant morbidity was assessed by the frequency of and reasons for hospitalization of newborn infants, and the occurrence of neonatal seizures in full-term babies within 48 h of birth as proposed by Dennis & Chalmers (1982).

Results

Place of birth

The 7980 women gave birth to 8055 infants (75 sets of twins). The place of birth after selection is shown in Table 1. In total, 5988 infants (74·3%) were born at home, in the maternity unit or (a minority) in a hospital under supervision of a midwife, 1430 infants (17·7%) were born in a hospital after referral of the mother during pregnancy, and 637 infants (7·9%) were born after referral during delivery.

Birthweight and gestational age

Birthweight distribution is shown in Table 2 and gestational age distribution in Table 3. Of the newborns, 4·9% had a birthweight <2500 g (6·0% of the nulliparous women, 3·5% of the parous women) and 4·4% a gestational age <259 days (5·5% of the nulliparous women and 3·3%

Table 2. Birthweight distribution of the 8055 babies in the total group and the selected (low-risk) group of 6625 babies

Birthweight (g)	Total group (*n*=8055) *n* (%)	Selected group (*n*=6625) *n* (%)
500–749	4 (0·05)	—
750–999	9 (0·1)	—
1000–1249	18 (0·2)	1 (0·01)
1250–1499	28 (0·3)	2 (0·03)
1500–1749	37 (0·5)	—
1750–1999	44 (0·5)	7 (0·1)
2000–2499	257 (3·2)	80 (1·2)
≥2500	7654 (95·0)	6535 (98·6)
Unknown*	4 (0·05)	—

*Probably ≥2000 g

Table 3. Gestational age distribution of the 8055 babies in the Wormerveer study in the total and selected (low-risk) group of 6625 babies

Gestational age Days (weeks)	Total group (*n*=8055) *n* (%)	Selected group (*n*=6625) *n* (%)
154–195 (22–27)	17 (0·2)	—
196–223 (28–31)	36 (0·4)	1 (0·01)
224–244 (32–34)	94 (1·2)	6 (0·09)
245–258 (35–36)	205 (2·5)	59 (0·9)
Subtotal	352 (4·4)	66 (1·0)
≥259 (≥37)	7431 (92·2)	6343 (95·7)
Unknown	272 (3·4)	216 (3·3)

Table 4. Caesarean section and operative vaginal delivery rates by parity in the total group of 7980 and the selected group of 6613 women

			Mode of delivery			
			Caesarean section		Operative vaginal*	
Parity	Total *n*	Selected *n*	Total *n* (%)	Selected *n* (%)	Total *n* (%)	Selected *n* (%)
0	4000	3092	80 (2·0)	21 (0·7)	344 (8·6)	230 (7 4)
≥1	3980	3521	30 (0·7)	8 (0·2)	24 (0·6)	18 (0·5)
Total	7980	6613	110 (1·4)	29 (0·4)	368 (4·6)	248 (3·7)

*Includes forceps and vacuum extraction.

of the parous women). In the selected group 1·4% of the newborns had a birthweight <2500 g, and 1·0% a gestational age <259 days.

Instrumental and operative deliveries

The instrumental and operative delivery rates in the total and selected group are shown in Table 4. The caesarean section rate was 1·4%, the rate of vacuum extractions and forceps deliveries was 4·6%. In the group selected for delivery under supervision of a midwife the caesarean section rate was 0·4%, the rate for vacuum extraction and forceps delivery was 3·7%.

In Table 5 the main indications for caesarean section in the total and selected groups are shown for nulliparous and parous women separately. In nulliparous women fetal distress was the most common indication for caesarean section both in the total and the selected groups (40 and 42·9% respectively). Disproportion, malposition and breech position taken together were the reasons for caesarean section in 45% of all nulliparous women. In the selected group of nulliparous women, disproportion and malposition were the indications for caesarean section in 42·9% of all cases.

In the parous women of the total group, blood loss and fetal distress were the two most important indications for caesarean section (40% and 30% respectively).

The main indications for instrumental vaginal deliveries are shown in Table 6. Poor progress in the second stage of labour was the most important reason for instrumental delivery in all groups (nulliparae: total group 72·7%, selected group 74·3%; parous women: total group 79·2%, selected group 83·3%).

Perinatal mortality

The mortality (≥22 weeks gestation and/or ≥500 g birthweight) comprised 89 deaths in 8055 children: 50 stillbirths and 39 early neonatal deaths. The highest perinatal mortality was found in the group of children born in a hospital after maternal referral by the midwife to a specialist obstetrician during pregnancy: 74 deaths in 1430 children (51·7/1000). The lowest mortality was found in the group of children born at home or in the maternity home under the supervision of a midwife: eight deaths in 5988 children (1·3/1000). The 6625 infants born to the group of women selected for delivery under the care of a midwife showed an overall perinatal mortality of 2·3/1000 (Table 1).

In Table 7 perinatal deaths are shown in relation to maternal, fetal and neonatal factors in the total and selected groups separately (after Cole *et al.* 1986; Hey *et al.* 1986).

Infant morbidity

The number of infants who had seizures within 48 h of birth at term was seven (0·9/1000 livebirths) in the total group, five (0·8/1000) in the selected group, and four (0·7/1000) in the group born under the sole care of a midwife. Table 8 shows the indications for admission to a paediatric department within a week of birth in the total group, the selected group and the group born under the sole care of the midwife; the rates of admission were 8·2%, 4·3% and 3·8%, respectively. Most admissions were for observation only. The main specific indications for admission were jaundice, 'asphyxia', congenital malformations and infections. Only 23 (0·4%) born under the sole care of a midwife were

Table 5. Main indications for caesarean section in the total group of 4000 and 3092 selected nulliparous women, and total group of 3980 and 3521 selected parous women

	Total group by parity		Selected group by parity	
Indication	0 *n* (%)	≥1 *n* (%)	0 *n* (%)	≥1 *n* (%)
Fetal distress				
Antepartum	10 (12·5)	2 (6·7)	—	—
During labour	18 (22·5)	6 (20·0)	8 (38·1)	2 (25·0)
During delivery	4 (5·0)	1 (3·3)	1 (4·8)	—
Disproportion				
Antepartum	1 (1·2)	—	—	—
During labour	15 (18·7)	1 (3·3)	3 (14·3)	—
Malposition	7 (8·7)	5 (16·7)	6 (28·6)	4 (50·0)
Breech	13 (16·2)	2 (6·7)	1 (4·8)	—
Prolapsed cord	7 (8·7)	1 (3·3)	2 (9·5)	1 (12·5)
Blood loss	3 (3·7)	12 (40·0)	—	1 (12·5)
Other	2 (2·5)	—	—	—
Total	80	30	21	8

Table 6. Main indications for instrumental vaginal deliveries in the total group of 4000 and 3092 selected nulliparous women, and total group of 3980 and 3521 selected parous women

	Total group by parity		Selected group by parity	
Indication	0 *n* (%)	≥1 *n* (%)	0 *n* (%)	≥1 *n* (%)
Signs of fetal distress	93 (27·0)	5 (20·8)	59 (25·6)	3 (16·7)
Poor progress in second stage	250 (72·7)	19 (79·2)	171 (74·3)	15 (83·3)
Eclamptic seizure during labour	1 (0·3)	—	—	—
Total	344	24	230	18

admitted immediately after birth because of 'asphyxia'. Of these 23 infants, 21 were born in the period 1969–1976, and only two during the period 1977–1983.

Discussion

Our results show that selection of pregnant women into groups at high and low risk is possible using the relatively modest means available to the midwife. One of the outcome variables in this study is the perinatal mortality rate. Of the total number (89) of perinatal deaths, 15 (16·8%) occurred in the group of 6625 infants (82·2%) born to women selected as low-risk cases, and 74 (83·1%) in the group of 1430 (17·7%) infants born to women selected as high-risk cases during pregnancy. Total perinatal mortality in the sample studied here is low compared with the national figures (1969–1983: 14·5/1000) (Netherlands Central Bureau of Statistics 1970–1987). However, a relatively low perinatal mortality was to be expected in our group of women because, especially among multiparae, the women with an unfavourable obstetric or medical history were referred by the general practitioner to the specialist early in pregnancy and did not book at the practice of freestanding midwives. The number and percentage of instrumental vaginal deliveries and caesarean sections was low, especially in the group of women selected as being low risk for delivery at home or in the maternity unit by midwives. During the course of time this proportion increased somewhat (in 1969 the rates of instrumental vaginal deliveries and caesarean section were 6·1 and 1·0%, respectively, in nulliparae, and 0·5% and 0·4% in parous women; in 1980 the corresponding rates were 12·8% and 3·5% in nulliparae, and 0·8% and 0·5% in parous women) but the

Table 7. Stillbirths and early neonatal deaths by maternal factors, and fetal and neonatal factors, in the total group and selected (low-risk) group, Wormerveer 1969–1983

	Perinatal deaths	
	Total group	Selected group
Factors	*n* (rate/1000)	*n* (rate/1000)
Maternal factors		
Congenital anomaly	19 (2·4)	4 (0·6)
Pre-eclampsia	17 (2·1)	4 (0·6)
Antepartum haemorrhage	8 (1·0)	1 (0·1)
Other and not known	10 (1·2)	2 (0·3)
Unexplained	35 (4·3)	4 (0·6)
Total	89 (11·1)	15 (2·3)
Fetal and neonatal factors		
Congenital anomaly	19 (2·4)	4 (0·6)
Asphyxia and trauma	49 (6·1)	11 (1·7)
Pulmonary immaturity and hyaline membrane disease	13 (1·6)	— —
Other and not known	8 (1·0)	— —
Total	89 (11·1)	15 (2·3)

Table 8. Reasons for admission to a paediatric department during the first week of life in infants in the total group of 8005 liveborn infants, selected group of 6615, and in the group of 5985 infants born alive under sole care of a midwife

Indication	Total group (*n*=8005)	Selected group (*n*=6615)	Born under sole care of midwife (*n*=5985)
Total admitted *n* (%)	652 (8·2)	286 (4·3)	228 (3·8)
'Asphyxia' at birth	41	29	23
Cyanosis ('asphyxia')			
Day 1	29	28	28
Days 2–6	4	4	3
Convulsions	8	4	4
Jaundice	75	64	52
Congenital malformations	41	22	19
Birth trauma	5	2	2
Infections	30	17	9
Observation only			
LBW (<2500 g)	242	59	47
VLBW (<1500 g)	44	1	1
At risk hypoglycaemia	13	7	7
Other	120	49	33

rates remained relatively low, especially when compared with the national figures which in 1969 corresponded to 4·6% and 2·2% in nulliparae and 1·2% and 2·0% in multiparae, and in 1980 to 11·0% and 6·0% in nulliparae and 2·3% and 3·7% in multiparae (Netherlands Central Bureau of Statistics 1984).

The low perinatal mortality rate in the selected (low-risk) group is in agreement with the findings of Treffers & Laan (1986) who, from a study of regional perinatal mortality and hospitalization at the delivery, concluded that the degree of hospitalization was not a major factor determining variations in regional perinatal mortality rates in the Netherlands. A low perinatal mortality rate, especially in the group selected during pregnancy as low-risk cases (2·3/1000), is an important result of our study. This low mortality rate has been attained in spite of a low rate of intervention by instrumental vaginal deliveries and caesarean sections. In the group selected during pregnancy as low-risk cases the caesarean section rate was 0·4% and the vaginal instrumental delivery rate 3·7%.

Of the infants born under the sole care of a midwife 3·8% were admitted to hospital during the first week of life. Emergency admission immediately after birth because of 'asphyxia' was necessary in 23 (0·4%), and all but two of these infants were born between 1969 and 1976. Early diagnosis of fetal distress improved apparently during the course of time with a consequent slight increase in caesarean section and instrumental deliveries. With respect to convulsions in the neonatal period, Dennis & Chalmers (1982) proposed the occurrence of neonatal convulsions in term infants during the first 48 h as an index of the quality of perinatal care. They found a rate of 1·7/1000 in term infants during the first 48 h and 4·2/1000 in the total group during the first week of life. In the Dublin trial of fetal monitoring one of the outcome variables was the frequency of neonatal convulsions (MacDonald *et al.* 1985).

In the total group of 13 084 infants the frequency of neonatal convulsions was 39 (3·0/1000). In the 'low-risk' group the frequency was 2·6/1000. In the present study the frequency of neonatal convulsions in term infants during the first 48 h was 0·9/1000 in the total group and 0·8/1000 in the selected group of liveborn infants.

Umbilical artery pH and neonatal neurological examination were also investigated in 175 infants born to women who booked for antenatal care during 1982 and 1983. The results of these studies provide further evidence of the successful selection achieved by the midwives (Eskes *et al.* 1987; Knuist *et al.* 1987).

The fact that a study was being conducted in Wormerveer and the elicited discussion with the midwives about perinatal problems are very likely to have influenced the quality of obstetric care. Nevertheless, the decision making, the indications for referral and the diagnostic facilities in the Wormerveer area are not different from those in other parts of the country, and the external investigators were careful not to interfere in the process of decision making and referral. The responsibility for selection and referral remained in the hands of the midwives, as in other parts of the country. The data available on perinatal mortality and infant morbidity warrant the conclusion that within the scope of the Dutch system of obstetric care it is possible to achieve very good results with midwifery care for selected women.

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Cytogenetic findings in 1250 chorionic villus samples obtained in the first trimester with clinical follow-up of the first 1000 pregnancies

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Summary. First-trimester chorionic villus sampling (CVS) was performed in a series of 1250 pregnancies. The direct method of karyotyping was successful in 1205 (96·4%). Abnormal laboratory findings resulted in 60 terminations of pregnancy (4·8%). In addition, six unexpected balanced chromosome rearrangements were detected. False-positive cytogenetic findings occurred in 2·3%, comprising 22 with mosaicism confined to the trophoblast, and a further six non-mosaic false-positive discrepancies were detected, four after termination of pregnancy. The outcome of the first 1000 pregnancies is known in all but one. There were no false-negative findings. Of 947 pregnancies meant to be continued, 34 (3·6%) ended in pregnancy loss before 28 weeks gestation. However, obstetricians with an experience of over 150 procedures had a pregnancy loss of 1·3%.

Chromosome analysis of chorionic villi cells in the first trimester of pregnancy has become a welcome alternative to mid-trimester amniocentesis for the prenatal diagnosis of chromosome disorders. However, descriptions of the results of chorionic villus sampling (CVS) are still scarce and we are not aware of detailed one-centre studies, in which the outcomes of at least 1000 pregnancies are reported.

We here report our cytogenetic and clinical findings in our first 1250 patients with complete follow-up data for the first 1000.

Patients and methods

Transcervical CVS was performed either with a Portex cannula, a Braun cannula, a silver cannula or a biopsy forceps (Wolf, Ø 3 mm) between 8 and 11 weeks gestation. Obstetricians from three university departments contributed to the study (Amsterdam 625, Leiden 379, Utrecht 219; a further 27 samples were received

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from an obstetrician in a non-academic hospital in Arnhem).

The direct method (Simoni *et al.* 1983) was used, with small modifications in all cases: all samples were stored overnight at −20°C after fixation. Specimens obtained in Leiden, Utrecht and Arnhem were processed as far as fixation in methanol/acetic acid before being sent to Amsterdam. The average time in transit was about 1 h.

Chromosomes were studied by Q-banding, and a minimum of 10 metaphases was analysed in each case. DNA studies for Duchenne muscular dystrophy and haemophilia A/B were performed at the Department of Human Genetics in Leiden (Professor Dr P. L. Pearson). The cytogenetic results are based on 1250 pregnancies from which a chorionic villus sample was received in the laboratory, and clinical follow-up data are based on the first 1000. To assess the risks of CVS this series of 1000 was augmented with data derived from the follow-up of 29 pregnancies investigated during the same period but from whom no chorionic villi could be obtained. Detailed analysis of pregnancy losses is restricted to patients with normal laboratory findings.

Results

Cytogenetic findings

Of the 1250 pregnancies investigated the main indication for CVS was advanced maternal age (defined as ≥36 years at the time of sampling) in 1051 (84%); other indications were X-linked disease (77), a previous child with a mutant chromosome aberration (72), a translocation in one parent (18), paternal age of ≥55 years (9), and a miscellaneous group of 23 pregnancies in 16 of which the maternal age was 35.

Successful karyotyping was possible in 1205 (96%). The distribution of inadequate samples did not differ substantially between the participating centres (Amsterdam 3·8%, Leiden 2·9%, Utrecht 4·5%). In 38 of these 45 pregnancies a normal fetal karyotype was found at amniocentesis, four women refused further examination, two miscarried, and in one with a risk of X-linked disease, fetal sex was determined by DNA study alone.

Abnormal laboratory findings resulted in 60 terminations of pregnancy (5%); in addition, six unexpected balanced chromosome rearrangements were detected. Mosaicism was present in 22 samples and was shown to be a false-positive finding in 21 after amniocentesis and in one after miscarriage. Furthermore six non-mosaic false-positive discrepancies were detected after termination of pregnancy in four and at amniocentesis in two (Table 1).

The overall sex ratio at the time of sampling, including both normal and abnormal karyotypes, was 606:599 (101·2).

Four case histories

Patient 47. This was a 38-year-old woman in her sixth pregnancy; she had given birth to four healthy daughters, and had one miscarriage. Indication for CVS was maternal age, and 40 mg chorionic villi were obtained at 9·4 weeks gestation. In all cells a small marker chromosome was present. Both parents were shown to have a normal chromosome complement. The parents refused a confirmatory amniocentesis. Abortion was carried out at 11·5 weeks. The marker chromosome was observed in cultured cells from the placenta, but cultured cells of fetal tissue had a normal (46,XX) chromosome complement. Pathological examination of some fetal parts revealed female reproductive organs and a foot length of 7 mm in conformity with the age of gestation.

Patient 103. This was a woman in her fourth pregnancy; she had given birth to one healthy daughter and one son with mental retardation associated with the fragile X syndrome (fra Xq (27)), one pregnancy was terminated after amniocentesis because of a male fetus (46,XY). CVS for fetal sex determination was performed at 9·4 weeks gestation, and 10 mg of chorionic villi were obtained. (Because of equivocal results in the literature we did not examine the cells for the abnormal X chromosome.) An abnormal Y chromosome was found in all cells, most probably due to the translocation of part of an unknown autosome to the long arm of the Y-chromosome. Since there was no doubt about the sex of the fetus, the pregnancy was terminated at 10·4 weeks. Only normal cells were found in cells cultured from both the placenta and the fetus.

Patient 891. This 36-year-old woman was in her third pregnancy; she had given birth to two healthy children. Indication for CVS was mater-

Table 1. False-positive cytogenetic findings in 28 chorionic villus samples (CVS)

Patient no.	CVS karyotype		Amniocyte karyotype	Outcome		
	Mosaic	Non-mosaic		Termination	Miscarriage	Continued*
47		47,XX,+mar	—	Fetus: 46,XX Placenta: 47,XX,+mar		
103		46,XYq+	—	Fetus: 46,XY Placenta: 46,XY		
113	46/47,XX,+12(7:5)		46,XX			N
130	46/47,XX,+5(8:7)		46,XX			N
162	46,XX/45,X/45,X,+mar		46,XX			N
210		92,XXYY	46,XY			N
222	45,X/46,XX(8:1)		46,XX			N
258	46/47,XX,+16(21:9)		—		Fetus: failed Placenta. 46,XX	
268	46,XY/92,XXYY(8:8)		46,XY			N
272	46/47,XY,+?19(15 2)		46,XY			N
277	46/47,XX,+mar (9·3)		46,XX			N
378		47,XX,+11	46,XX			N
411	46/50,XY,+2,+3,+7,+15(28:5)		46,XY			N
428	46/47,XY,+7(12 3)		46,XY			N
495	46/46,XX,5p+(14:2)		46,XX			N
637	46,XX/47,XXX(8:3)		46,XX			N
722	46/47,XX,+20(4·6)		46,XX			N
733	46/45,XY,−11(10:4)		46,XY			N
755	46/47,XY,+18(14.3)		46,XY			N
875	46,XX/45,X(14:2)		46,XX			N
889	46/47,XX,+21(13:1)		46,XX			N
891		45,X	—	Fetus: 46,XY Placenta: 45,X/46,XY		
914	46,XY/92,XXYY(±50%)		46,XY			†
958		47,XX,+18	—	Fetus: 46,XX Placenta: 46,XX		
1030	46/47,XX,+18(14:2)		46,XX			N
1041	46/47,XY,+mar(10:2)		46,XY			N
1193	46,XY/45,X(11:2)		46,XY			P
1221	46,XX/92,XXXX (70%:30%)		46,XX			P

* N, Normal; P, Pending

† Induced abortion for psychosocial reasons.

nal age, and at 10 weeks gestation 15 mg of chorionic villi were obtained. A 45,X karyotype was found in all cells. The parents refused confirmatory amniocentesis and the pregnancy was terminated at 12·5 weeks. Cultured fetal cells revealed a normal male karyotype (46,XY). Cultured placental cells from two placenta biopsies after the abortion revealed a mosaic pattern—45,X/46,XY(12:3)—in one biopsy, while cells cultured from a second biopsy all had a normal (46,XY) karyotype ($n=15$).

Patient 958. This 37-year-old woman was in her second pregnancy; she had one healthy child. Indication for CVS was maternal age, and at 9·1 weeks gestation 100 mg of chorionic villi were obtained. At 7 weeks ultrasound had revealed a small sonolucent area adjacent to the amniotic sac containing the living fetus. This area had disappeared at the time of CVS. All 15 cells showed a trisomy 18 (47,XX,+18). The pregnancy was terminated at 10·4 weeks by suction curettage. Cultured cells from both placenta and fetus had a normal chromosome content (46,XX), but no recognizable fetal parts were seen after the abortion. We were concerned by these results and to exclude an error in labelling a confirmatory amniocentesis was performed subsequently in another woman who had had CVS in the same hospital on the same day. The normal CVS findings in the latter patient were confirmed after the amniocentesis.

Maternal age ≥36 years. The abnormal findings by year of age in the 1051 women aged ≥36 years are listed in Table 2. (A total of 36 double indications is included in this category.) If autosomal and gonosomal aberrations are taken together the overall risk was 34/1051 (3·2%). Two pregnancies ended in miscarriage and one was continued despite the finding of trisomy 18. The other 31 pregnancies were terminated.

X-linked disease. Most of the 77 women in this group were at risk because of Duchenne muscular dystrophy (n=30) or haemophilia (n=30). Our findings are listed in Table 3. Pregnancy was terminated in 26 patients, including one with a female fetus, with a trisomy 21. The fetus was shown to be 'affected' by additional DNA (or other) studies in 17 of the 25 male fetuses.

Parental translocations. Our findings when CVS was performed for this indication in 18 women are listed in Table 4. There were six balanced translocations. Two pregnancies were terminated because of an unbalanced translocation (11%).

Other indications. Of the 104 pregnancies in this

Table 2. Abnormal findings by maternal age in 1051 pregnancies investigated for advanced maternal age

Maternal age (years)	n	Abnormal findings		Balanced chromosome aberrations	Patients with false-positive findings (nos)
		Autosomal	Gonosomal		
36	254	+18 +21	47,XXX 47,XXY 45,X*	inv(1)(p11;q12)mat t(13q14q)pat	113,411,428,875,889
37	251	+18(2)† +21 der(18)‡	47,XXY	t(1;5)(q23;q23)mat t(1;8)(p31;q24)mat	162,210,268,277,637, 1041,1221
38	207	+13 +21(3) +mar*		t(13q14q)mat	272,495,733,755 1193
39	139	+21(5)			
40	109	+18(2) +21(3)			130,222,378
41	49	+13 +18§ +21(2)			258,914
42	21	+21			
43	16	+18 +21			
44	3	+18¶ +21			
45	2				
Total	1051	30	4	5	22

* Diagnosis confirmed in placenta only (patients 47 and 891).

† Diagnosis (once) not confirmed after abortion (patient 958).

‡ Miscarriage 13 weeks.

§ Miscarriage 10 weeks.

¶ Pregnancy continued, diagnosis confirmed after birth.

Table 3. Abnormal findings in 77 pregnancies investigated for X-linked disease

		Laboratory findings					
		Female fetus		Male fetus		Outcome	
Indication	*n*	46,XX	Other	46,XY	Other	Continued	Termination
Male fetus at risk	74	34	Trisomy 21[*] 46/47,XX,+20[†]	36	DNA only[*] 46,X,Yq+[*]	48[‡]	26[§]
Female fetus at risk	3[¶]	1[‖]	—	2	—	3	—
Total	77	35	2	38	2	51	26

[*] Termination.

[†] Continued (patient 722: see Table 1).

[‡] Of which 13 were male, 11 after DNA analysis, one after ultrasound and one after fetal blood sampling.

[§] Of which 17 after DNA analysis.

[¶] Two: adrenal hyperplasia; one: familial breast cancer.

[‖] Treatment for adrenal hyperplasia started during pregnancy.

group 72 were investigated because of a chromosome aberration in a previous child (42 because a previous pregnancy was associated with trisomy 21). We found one (1%) recurrence of trisomy 21; the pregnancy was terminated and our findings were confirmed after the termination. In one pregnancy a variant chromosome (22p+) was shown to be of paternal origin. In nine pregnancies investigated because of paternal age of 55 or over, no abnormalities were detected and this was also true for the 23 pregnancies investigated for miscellaneous indications.

Outcome of pregnancies

Of the first 1000 pregnancies 49 were terminated because of abnormal laboratory findings. Two further pregnancies with an abnormal chromosome pattern ended in miscarriage. Two women had a miscarriage before amniocentesis could be performed after failure or after equivocal results of CVS karyotyping. In 32 pregnancies a normal karyotype was found after amniocentesis after an inadequate chorionic villus sample.

The outcome of the 947 pregnancies meant to be continued after normal laboratory findings had been established (either after CVS or amniocentesis) is shown in Table 5 (including one patient who refused amniocentesis but had a normal outcome of pregnancy). The perinatal death rate (all stillbirths of >28 weeks gestation and first-week neonatal deaths) was 0·3%. Congenital malformations were found in 1·6%. There were no false-negative findings.

Thirty-four pregnancies ended in pregnancy loss before 28 weeks (3·6%). In another 29 women (seen during the same period), in whom no chorionic villi could be obtained, four preg-

Table 4. Abnormal findings in 18 pregnancies investigated for parental translocation

		CVS karyotype		
Type of translocation	Translocation carrier P/M	Normal karyotype	Balanced translocation	Unbalanced translocation
Robertsonian	P: 2	1	1	—
	M: 6	3[*]	3	—
Reciprocal	P: 6	5	1[*]	—
	M: 4	1	1	2[†]
	18	10	6	2

[*] (Once) after amniocentesis.

[†] Both confirmed after abortion.

Table 5. Outcomes in 947 pregnancies meant to be continued after normal laboratory findings*

Category	*n*	Comments
Other terminations	7	Six for psychosocial reasons and one for Kell isoimmunization
Miscarriage (<20 weeks)	27	Five had signs of intrauterine infection
Preterm delivery		
20–28 weeks	9	Two livebirths
28–36 weeks	42	Two perinatal deaths (no. 422· female, 2070 g, 32 weeks, intrapartum stillbirth; no. 935: male, 2500 g, 35·6 weeks, intrauterine death); one baby with ventricular septal defect (no. 207, female, 1960 g. 36 weeks)
Term delivery (≥37 weeks)	861	One neonatal death at 6 days (no. 90: female, 2000 g, 37 weeks, heart disease); 14 with congenital malformations†
Lost to follow-up	1	

* Excluding four pregnancies with a (possible) abnormal karyotype.

† These 14 infants included four who were small-for-gestational-age; six with minor malformations; no 261. diaphragmatic hernia; no. 608: multiple congenital malformations; no. 673: congenital heart disease; no. 983: polycystic kidneys.

nancies were lost before 28 weeks. The overall risk is therefore 38/(947+29)=3·9%. The first mentioned 34 pregnancy losses (with normal laboratory findings) were further analysed. Chronologically 21 of these occurred in the first 500 patients and 13 in the second 500 patients. Of the 338 pregnancies biopsied with the forceps, four were lost before 28 weeks (1·2%); of the 662 pregnancies sampled with a cannula, 30 (4·5%) were lost before 28 weeks.

The experience of the nine obstetricians involved in this series is shown in Fig. 1. Obstetricians A, D and F predominantly used the forceps method, the others used a cannula exclusively. Two obstetricians performed more than 250 procedures. Though the results of obstetrician A suggest a 'learning curve', the results of obstetrician B were better from the start. If these individual differences and the different methods used are disregarded, obstetricians with an experience of over 150 CVS procedures had a risk of pregnancy loss before 28 weeks of 1·3%.

Discussion

Compared with amniocentesis the advantages of CVS as a method for the detection of fetal chromosome aberrations are obvious, but the possibility of false-positive findings can cause much anxiety for both patients and doctors. In four women in our series a chromosome aberration

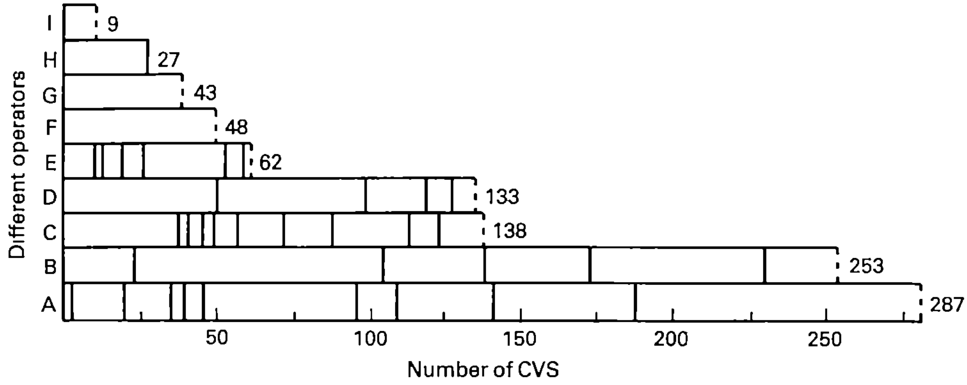

Fig.1. Individual experience of nine obstetricians (A–I) with 1000 chorionic villus samplings(CVS). Each bar represents a miscarriage before 28 weeks (*n*=34).

was not confirmed in fetal tissues after the termination of pregnancy. In two pregnancies the abnormality was found subsequently only in cultured placental cells; this suggests mosaicism confined to the trophoblast. The pregnancy with the Yq+ chromosome would have been terminated in any case because of the presence of a Y chromosome. The trisomy 18 discrepancy was most probably due to the vanishing twin phenomenon (Landy *et al.* 1986); however, mosaicism (46,XX/47,XX,+18) with abnormal cells only in the placenta can not be excluded. Although later amniocentesis revealed normal findings in 23 patients, the emotional burden of 8 weeks uncertainty should not be underestimated, especially if the couple had opted for CVS because of the early gestation at which the procedure can be performed. On the other hand there were no false-negative findings among the first 1000 consecutive pregnancies of which the outcome is known.

In two recent studies (Kalousek *et al.* 1987; Crane & Cheung 1988) the problem of mosaicism confined to the chorion is discussed. Usually mosaicism is found only in direct chromosome preparations, due to post-zygotic non-disjunction limited to cytotrophoblast (Crane & Cheung 1988). When villus tissue is trypsinized and cultured, the cells used for cytogenetic diagnosis are derived from the (extra) embryonic mesoderm (Kalousek *et al.* 1987). Crane & Cheung (1988) suggest the combined use of both direct chromosome preparations and villus cultures. In our experience mid-trimester amniocentesis to investigate suspect false-positive findings in direct chromosome preparations has been an acceptable procedure, and the workload is less than when both techniques are used for every sample.

We were surprised that six pregnancies in our series were terminated for other reasons, despite the presence of a normal chromosome complement. An inspection of the obstetric histories of these women suggests that the gender of the fetus is unlikely to have played an important role in this decision. Brambati *et al.* (1987) reported the same phenomenon in 12 patients in a series of 1000 patients. Detailed follow-up studies after CVS will teach us more about the frequency of these abortions and the motives of the women involved.

The risk of CVS is an important factor in counselling prospective patients: in our series of 1000 consecutive pregnancies, 34 pregnancies with a normal chromosome pattern ended in miscarriage or preterm delivery before 28 weeks gestation (3·6%). If the follow-up of 29 pregnancies in which no chorionic villi were obtained is included this figure changes to 3·9%. Because of the individual differences between the nine obstetricians involved (Fig. 1) and between the methods used, conclusions can only be tentative at this stage. Our results suggest that pregnancy loss after CVS is related to the experience of the obstetrician. We demonstrated the same phenomenon in assessing the risks of mid-trimester amniocentesis (Leschot *et al.* 1985). Although it is reassuring that the results of CVS may improve with experience, these results clearly show a procedure-related risk of miscarriage. Brambati *et al.* (1987) also stated 'that growing experience of the operators can certainly explain improving results', and their overall pregnancy loss up to 28 weeks of 25/615 (4·1%) is in the same range as our 3·9%. Green *et al.* (1988) mentioned a procedure-related fetal loss of approximately 0·6%. This figure is comparable with the 1·3% in our series for obstetricians with experience of at least 150 CVS procedures. It is concluded that before every CVS the procedure-related risk of miscarriage of about 1–2% and the 2% possibility of equivocal findings (including the need of subsequent amniocentesis) should be discussed with the couple It should be considered to include the possibility of gynaecological failure in obtaining villi (2·9%) and inadequate samples (3·4%) in this discussion

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Factors influencing neonatal morbidity in gestational diabetic pregnancy

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Summary. The influence of obstetric factors and indices of maternal blood glucose control on neonatal morbidity was examined in 261 women with gestational diabetes. A reference group of 218 women, matched for age and day of delivery, within 1 week, was used for comparison. Perinatal morbidity was significantly more frequent in the gestational diabetic pregnancies (23%) than in the reference group (13%), whereas the occurrence of large-for-gestational-age infants was not different between the groups. Infants born to women with gestational diabetes were categorized to a no-morbidity group (n=200) and a morbidity group (n=61). The group with morbidity had significantly shorter gestational age at delivery, higher frequency of caesarean section, higher maternal pre-pregnancy weight and higher area under the glucose tolerance curve. There was no significant difference in third-trimester blood glucose between the groups. Discriminant analysis revealed that the most significant influence on neonatal morbidity was gestational age at delivery. After correction for this factor the only factor with added significance for neonatal morbidity was maternal pre-pregnancy weight. The present study clearly illustrates that other factors beside blood glucose control are of importance for neonatal outcome in gestational diabetic pregnancy.

It is well established that pregnancies complicated by type 1 diabetes are of great clinical importance but opinions differ about pregnancies complicated by impaired glucose tolerance or gestational diabetes (Jarrett 1981; Beard & Hoet 1982). Even a moderate impairment of glucose tolerance has been reported to be associated with elevated plasma levels of glucose, free fatty acids, glycerol, beta-hydroxybutyrate, triglycerides and branched chain amino acids (Gillmer *et al.* 1975; Persson & Lunell 1975; Metzger *et al.* 1980). Available data suggest that such maternal metabolic abnormalities may lead to fetal hyperinsulinaemia (Freinkel & Metzger 1979). Exaggerated fetal insulin secretion has been considered to be one important mechanism contributing to fetal macrosomy, delayed fetal lung maturation and neonatal hypoglycaemia (Pedersen 1977; Persson 1978; Ogata *et al.* 1980).

The results of previous studies also suggest that gestational diabetes is associated with increased risk of fetal macrosomia, birth trauma, neonatal hypoglycaemia, hyperbilirubinaemia and respiratory disorders (Gabbe *et al.* 1977; Warrner & Cornblath 1969).

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In a recent study Persson *et al.* (1985) compared the effect of two treatment regimens, diet alone and diet plus insulin, on perinatal outcome in pregnancies complicated by gestational diabetes and found no significant differences, there were no perinatal deaths but neonatal morbidity was recorded in 29% of the infants.

The object of the present study was to assess in more detail the influence of obstetric factors and indices of maternal blood glucose control on neonatal morbidity.

Subjects and methods

Since 1981 systematic screening for gestational diabetes has been conducted within the catchment area of the Karolinska Hospital. Women with a family history of diabetes, a previous baby with birthweight >4500 g, a previous stillbirth or neonatal death, obesity during the index pregnancy, glycosuria, signs of excessive fetal growth, polyhydramnios or a random blood glucose value >6·5 mmol/l, were subjected to an oral glucose tolerance test (OGTT). The diagnosis of gestational diabetes was based on the results of a 3-h 50-g oral glucose tolerance test. An area under the glucose curve equivalent to ⩾42 mmol/l was considered as pathological (Gillmer *et al.* 1975).

Gestational diabetes

The present analysis includes 268 women with gestational diabetes (GD) diagnosed between 1981 and 1984. These women took part in a prospective randomized study which compared the effect of diet alone and diet and insulin in the treatment of gestational diabetes (Persson *et al.* 1985). Altogether 117 GD patients were randomized to treatment with diet, and 106 to treatment with insulin and diet. Thirty-eight (38) women refused to participate in the randomized study and were initially treated with diet alone. Data for seven women were incomplete and they were excluded from the analysis.

Reference group

A sample of 218 women was selected to match the GD group with regard to maternal age (same year of birth) and date of delivery, within 1 week.

Obstetric care

All patients were given routine antenatal care and were seen every second week in the outpatient clinic; weight gain, haemoglobin and blood pressure were continuously recorded. Pregnancy-induced hypertension (PIH) was defined as blood pressure >140/90 mmHg. Preeclampsia was diagnosed if proteinuria or oedema also occurred. Gestational age was calculated from the first day of the last menstrual period. Preterm labour was not induced unless there were acute severe pregnancy complications.

Blood glucose control in GD patients

All GD patients were instructed about self-monitoring of blood glucose at diagnosis. Blood glucose values were determined before and after each meal, six times a day, three days a week, using reagent strips and reflectance meters. Management with diet alone was considered inappropriate if fasting or 1-h postprandial blood glucose values exceeded 7 or 9 mmol/l, respectively, more than three times during 1 week. Insulin treatment was then started. Insulin treated patients were given 8–12 IE/day of fast- or intermediate-acting insulin routinely. Insulin doses were adjusted according to blood glucose values aiming at fasting and postprandial blood glucose values of 5 and 6·5 mmol/l, respectively. HbA_{1c} was determined at diagnosis and at the time of delivery by isoelectric focusing (Jepson *et al.* 1980).

Neonatal care

All infants were observed in the delivery ward for about 2 h. Apgar scores at 1 and 5 min and birthweight and length were recorded.

Reference group. Routine examination by a paediatrician was made within the first 24 h after birth. Healthy infants were then observed in the maternity ward, and no routine blood tests were made in infants without symptoms.

GD group. All infants were observed in the neonatal unit for at least 24 h. At delivery umbilical cord serum was taken for determination of C-peptide (Heding 1975). Blood samples for haemoglobin, haematocrit and blood glucose were obtained about 2 h after birth. Blood glucose was then determined every 4 h during the first 24 h. Early feeding was practised (Persson *et al.* 1975).

Definition and classification of morbidity

Respiratory disorders were classified according to the criteria stated by Hjalmarson (1981). A haematocrit value >70% was regarded as polycythaemia. Symptomatic hypoglycaemia was defined as a blood glucose value <1·7 mmol/l where administration of intravenous glucose gave relief of symptoms. Hyperbilirubinaemia was defined as a serum bilirubin value above 300 μmol/l or as a hyperbilirubinaemia requiring treatment (phototherapy or exchange transfusion). Feeding problems were considered to be present if the early feeding programme could not be followed or if the infant required nasogastric feeding. Babies were categorized as large for gestational age (LGA), defined as a birthweight more than 2 SD above the mean, small for gestational age (SGA), a birthweight more than 2 SD below the mean, and appropriate for gestational age (AGA), a birthweight of mean ± 2 SD, according to Swedish standards.

Statistical methods

For comparison of samples from two independent groups the Mann–Whitney *U*-test was used. To measure association between independent variables the Spearman rank correlation test or multiple linear regression was used. To compare different distributions the χ^2-test was used. Discriminant analysis was used to determine which factor had the greatest impact on the classifications to different groups.

Results

Maternal and infant data for all patients in the GD and reference groups are presented in Table 1. There were significantly more nulliparae in the reference group (87) than in the GD group (49) ($P<0{\cdot}001$). Obesity was significantly more common in the GD group ($P<0{\cdot}001$).

The most frequent pregnancy complications were PIH and pre-eclampsia which occurred in 39 women with GD compared with 15 women in the reference group, the difference was statistically significant ($P<0{\cdot}01$). Of the 261 women with GD, 52 (20%) were delivered by caesarean section compared with 25 of 218 (11%) in the reference group, a significant difference

Table 1. Clinical data on women with gestational diabetes (GD) and a reference group

	GD group	Reference group	*P**
No. of subjects	261	218	
Maternal data			
Age (years)	31 (16–46)	31 (19–44)	NS
Pre-pregnancy weight (kg)	60 (39–130)	59 (42–90)	<0·01
Nulliparae	49 (19%)	87 (40%)	<0·0001
Obesity (BMI <1·6)†	65 (24%)	14 (6%)	<0·001
Pre-eclampsia and PIH	39 (14%)	15 (7%)	<0·01
Caesarean section	52 (19%)	25 (11%)	<0·025
Infant data			
Gestational age at delivery (days)	276 (211–297)	280 (220–298)	<0·001
Preterm birth (<37 weeks)	26 (10%)	12 (5·5%)	NS
Birthweight (g)	3530 (1465–4830)	3430 (1175–4830)	NS
Large-for-gestational-age‡	27 (10%)	15 (7%)	NS
Morbidity present	61 (23%)	29 (13%)	<0·01

Values are given as medians (range) or *n* (%) as appropriate

PIH, Pregnancy-induced hypertension.

* Mann–Whitney *U*-test or χ^2-test.

† BMI, Body-mass index calculated as $\frac{\text{weight (kg)} \times 10^5}{\text{height (cm)}^3}$.

‡ Defined as >2 SD above the mean birthweight.

($P<0\cdot025$). The overall caesarean section rate in this clinic during the study period was 11%. There was no perinatal mortality. In the GD group 61 of 261 infants (23%) showed morbidity compared with 29/218 (13%) in the reference group ($P<0\cdot01$). The different diagnoses are listed in Table 2.

The frequency of large-for-dates infants was not significantly higher in the GD group than in the reference group (Table 1).

Obstetric factors in relation to neonatal morbidity in the GD group are presented in Table 3. There were statistically significant differences both in maternal pre-pregnancy weight, gestational age at delivery and infant birthweight between the no-morbidity and the morbidity groups. There was a significant difference in neonatal morbidity between the GD group and the reference group for infants born between 37 and 40 weeks gestation ($P<0\cdot01$) but not for those born after 40 weeks (Table 4). Metabolic factors such as gestational age at diagnosis of GD, HbA_{1c} and third-trimester blood glucose control in relation to neonatal morbidity are presented in Table 5. OGTT area was the only factor which differed significantly between the groups. There was a correlation between third-trimester blood glucose and OGTT area ($r=0\cdot22$, $P<0\cdot001$) but no statistical difference could be shown in mean third-trimester blood glucose between patients with or without neonatal morbidity. Third-trimester blood glucose was correlated with infant birthweight ($r=0\cdot14$, $P<0\cdot05$), but no correlation was found with umbilical cord C-peptide ($r=0\cdot02$). Neither was HbA_{1c} at diagnosis or at delivery correlated with umbilical cord C-peptide.

Neonatal morbidity was not more frequent in the large-for-dates infants than in the AGA infants (Table 6). However, maternal pre-pregnancy weight, OGTT area, third-trimester blood glucose and cord C-peptide were all significantly higher in the LGA group (Table 6). Multiple regression analysis of these factors showed that maternal pre-pregnancy weight had the highest correlation ($r=0\cdot21$) with infant birthweight, which was also true for the reference group ($r=0\cdot15$).

Discriminant analysis

Since several factors are dependent on each other, discriminant analysis was used to determine which factors had the greatest impact on neonatal morbidity. The following factors were included in the analysis: gestational age at delivery, infant birthweight, OGTT area, maternal pre-pregnancy weight, mode of delivery and mean third-trimester blood glucose. The discriminant analysis revealed that the gestational age at delivery had the most significant ($P<0\cdot01$) influence on the occurrence of neonatal morbidity. After correction for this factor maternal pre-pregnancy weight was the only remaining factor that added significance ($P<0\cdot05$). The same analysis was done in the reference group including factors as maternal pre-pregnancy weight, gestational age at delivery and mode of delivery. This analysis showed that gestational age at delivery was the only factor with significant influence on neonatal morbidity ($P<0\cdot001$).

Discussion

In the present study the frequency of perinatal morbidity was significantly higher ($P<0\cdot01$) in pregnancies with GD compared with an age-matched reference group. This finding agrees with the observations of others (Gabbe *et al.* 1977; Mestman 1980) who have reported about 25% neonatal morbidity in class A diabetic preg-

Table 2. Neonatal complications in infants born to women with gestational diabetes (GD) and a reference group

Diagnosis	GD group (n=261) n	Reference group (n=218) n	P
Respiratory disorders	25	13	NS
Feeding problems	12	1	<0·01
Symptomatic hypoglycaemia	2	0	NS
Bilirubinaemia requiring treatment	17	12	NS
Polycythaemia (haematocrit >70%)	11	3	NS

$P=\chi^2$-test.

Table 3. Obstetric factors in relation to occurence of neonatal morbidity in women with gestational diabetes

	Neonatal morbidity		
	Absent	Present	P*
No. of subjects	200	61	
Maternal pre-pregnancy weight (kg)	60.0 (39·0–130·0)	65 (40·0–110·0)	<0·05
Obesity (BMI 1·6)	44 (21%)	21 (35%)	NS
Pre-eclampsia and PIH	25 (12·5%)	13 (21%)	NS
Caesarean section	33 (16%)	19 (30%)	<0·025
Gestational age at delivery (days)	277 (234–297)	271 (230–284)	<0·001
Preterm birth (<37 weeks)	13 (6%)	12 (20%)	<0·01
Infant birthweight (g)	3350 (1900–4830)	3420 (1465–4630)	<0·01
Large-for-dates	18 (9%)	9 (15%)	NS

Values are given as medians (range) or n (%) as appropriate.
* Mann–Whitney U-test or χ^2-test.
See Table 1 for abbreviations and definitions.

nancies. It has, however, been questioned whether maternal hyperglycaemia in GD is the cause for fetal risk or whether impaired glucose tolerance is associated with other risk factors (Jarrett 1981).

Obesity was significantly more common among GD patients than in the reference group, as could be expected since overweight was used as one selection criterion for OGTT, which is in accordance with other studies (Mestman *et al.* 1971; O'Sullivan *et al.* 1966). In the GD group, maternal pre-pregnancy weight was significantly higher in the pregnancies associated with neonatal morbidity than in the no-morbidity group; this agrees with earlier reports by O'Sullivan *et al.* (1973) and Sutherland *et al.* (1978). This is also supported by results of the discriminant analysis which show that besides gestational age at delivery maternal pre-pregnancy weight was the only factor with impact on the classification of neonatal morbidity.

The fact that the caesarean section rate was significantly higher in the GD group than in the reference group was mainly due to a higher frequency of acute pregnancy complications such as pregnancy-induced hypertension and pre-eclampsia. This mode of delivery has been reported to cause more transient respiratory disorders than vaginal delivery (Faxelius *et al.* 1983), but we could find no correlation between mode of delivery and neonatal morbidity. The most frequent neonatal complications in the present study were respiratory disorders, hyperbilirubinaemia and polycythaemia, which agrees with others (Warrner & Cornblath 1969; Gabbe *et al.* 1977; Mestman 1980). Previous studies have shown that the occurrence of macrosomia varies between 20 and 25% in GD patients depending on the definition used (Gabbe *et al.* 1977; Coustan & Lewis 1978; Gyves *et al.* 1977, 1980). We found no significant difference in the occurrence of large-for-dates infants between GD patients (10%) and the reference group (7%); this could be attributed to the rigid blood glucose control or to the possibility that many GD patients had only a moderate deviation in glucose tolerance or to the fact that 20% of our GD patients did not start treatment before 35 weeks gestation.

Many investigators (O'Sullivan 1975; Gyves *et al.* 1980; Roversi *et al.* 1980; Coustan & Imarah 1984) have suggested that insulin therapy of gestational diabetes has a beneficial influence on both neonatal morbidity and macrosomia. How-

Table 4. Frequency of neonatal morbidity according to gestation in infants born after 37 weeks gestation to women with gestational diabetes (GD) and a reference group

Gestational age at delivery (weeks)	GD group n/n (%)	Reference group n/n (%)	P
37–40	44/172 (25)	12/105 (11)	<0·002
>40	7/69 (10)	7/100 (7)	NS
P	<0·04	NS	

χ^2-test.

Table 5. Metabolic factors in relation to occurrence of neonatal morbidity in women with gestational diabetes (GD)

	No morbidity	Morbidity	*P**
No. of subjects	200	61	
Gestational age at diagnosis (days)	233 (62–297)	221 (72–278)	NS
OGTT area (mmol/l)	44·3 (42·0–76·0)	45·7 (42·0–54·7)	<0·05
HbA$_{1c}$ at GD diagnosis (%)	6·6 (5·0–9·4)	6·7 (5·5–10·0)	NS
HbA$_{1c}$ at delivery (%)	7·1 (5·2–9·3)	6·8 (6·1–9·9)	NS
Third-trimester blood glucose (mmol/l)	5·5 (3·1–8·5)	5·6 (3·7–7·6)	NS
C-peptide in umbilical cord (nmol/l)	0·20 (0·05–2·35)	0·23 (0·06–0·79)	NS

* Mann–Whitney *U*-test.
Values are given as medians (range).

ever, as reported earlier (Persson *et al.* 1985) we found no significant difference in the frequency of neonatal complications or large-for-gestational-age infants between diet-treated or insulin-and-diet-treated GD patients. The design of the study may explain this finding as diet-treated patients who had blood glucose values in fasting or postprandially exceeding 7 or 9 mmol/l, respectively, were given insulin treatment, although these blood glucose values were slightly higher than those recommended by the Second Workshop on Gestational Diabetes (1985) (5·8 and 6·6 mmol/l) for insulin therapy. The fact that both HbA$_{1c}$ at delivery and C-peptide in umbilical cord were almost identical and not different from reference values in healthy controls suggests that a good equivalent degree of metabolic control was achieved in all GD patients irrespective of treatment regimen. However, even a slight rise in blood glucose has been reported to be accompanied by a greater frequency of macrosomia (Tallarigo *et al.* 1986). This could not be confirmed in this study. Instead, multiple regression analysis showed that the influence of OGTT area and maternal third-trimester blood glucose on birthweight lost significance when corrected for maternal pre-pregnancy weight. Our observation that maternal pre-pregnancy weight had a significant impact on infant size at birth agrees with previous reports (Peckham & Christianson 1971; Abrams & Laros 1986; Langhoff-Roos 1987). Since most factors associated with neonatal morbidity are inter-related, discriminant analysis is appropriate to use to determine which factor has the greatest impact on neonatal outcome. This

Table 6. Obstetric and metabolic data for women with gestational diabetes (GD) in relation to infant birthweight

	Large-for-dates (*n*=27)	Appropriate-for-dates (*n*=234)	*P**
Maternal data			
Age (years)	30 (22–46)	31 (16–42)	NS
Nulliparae	2 (8%)	44 (19%)	NS
Pre-pregnancy weight (kg)	71 (52–130)	60 (39–129)	<0·001
Obesity (BMI >1·6)	9 (30%)	52 (22%)	NS
Gestation at diagnosis (days)	238 (91–288)	230 (62–297)	NS
OGTT area (mmol/l)	46·5 (43·1–64·8)	44·5 (42·0–76·0)	<0·025
Third-trimester blood glucose (mmol/l)	5·84 (3·86–8·47)	5·49 (3·14–7·57)	<0·025
Infant data			
Gestational age (days)	277 (251–291)	276 (211–297)	NS
Birthweight (g)	4330 (2830–4830)	3465 (1465–4400)	—
Cord C-peptide (nmol/l)	0·26 (0·10–1·36)	0·20 (0·05–2·35)	<0·05
Morbidity present	9 (30%)	52 (22%)	NS

Values are given as medians (range) or *n* (%) as appropriate.
* Mann–Whitney *U*-test or χ^2-test.
For abbreviations and definitions see Table 1.

study clearly demonstrates that gestational age at delivery was the most important single factor influencing neonatal morbidity while, within the range of blood glucose levels achieved, there was no association between indices of maternal blood glucose control and neonatal morbidity. The morbidity recorded was of minor clinical significance in the majority of cases, probably due to the fact that most of the patients were delivered at or near term. Interestingly, there is a significant difference in neonatal morbidity between GD patients and the reference group even after 37 completed weeks gestation but not after term. One could speculate that this difference in neonatal morbidity could be attributed to a relative immaturity in GD infants and, thus, further emphasizes the importance of not inducing labour before full term.

In conclusion, the present observation illustrates that women with gestational diabetes represent a heterogeneous group and that other factors beside blood glucose control have an important and significant influence on fetal and neonatal well-being.

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Obstetric acute renal failure 1956–1987

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Summary. A total of 142 women with severe acute renal failure (ARF) resulting from obstetric causes was treated by dialysis at a single centre from 1956 to 1987. One-year survival was 78·6%, which compares favourably with other causes of ARF. Abortion, haemorrhage and pre-eclampsia comprised 95% of cases, with survival being best (82·9%) with abortion. Survival was adversely affected by increasing age. Acute cortical necrosis (12·7% of patients) carried 100% mortality after 6 years. Follow-up of survivors showed normal renal function up to 31 years following ARF; 25-year patient survival was 71·6%. Improvements in obstetric care and the disappearance of illegal abortions have resulted in a dramatic decline in the incidence of obstetric ARF.

Standard sources suggest that about 10–20% of all acute renal failures (ARF) occur in relation to pregnancy and its complications (Brenner & Lazarus 1983). However, recent experience has shown that pregnancy is now a rare cause of ARF in Britain (Wheeler *et al.* 1986; Beaman *et al.* 1987). We have performed a retrospective analysis of more than 1300 cases of ARF treated by dialysis at a single centre since 1956. The early experience of the management of ARF at this unit has been reported previously (Parsons & McCracken 1958; Parsons 1963). This survey includes only those patients with severe renal failure, most of whom required dialysis therapy, mainly by haemodialysis. Of these cases, 142 (10·54%) occurred in an obstetric setting. We present a retrospective analysis of these patients.

Patients and methods

We have identified and, whenever possible, analysed the hospital records of 1347 patients with ARF treated at The General Infirmary at Leeds from September 1956 to October 1987. Patients were identified from the Renal Unit dialysis records, and the original hospital notes were obtained and scrutinized. Follow-up data were obtained from the referring hospital and general practitioners. These data are necessarily incomplete for the earlier cases because of the policy of destruction of old case records at some hospitals.

This study includes only obstetric patients with serum creatinine concentrations >600 μmol/l (6 mg/dl) or urea >30 mmol/l (180 mg/dl) or requiring dialysis or both. The dialysis rate varied between 85% and 100%, with over 90% being treated by haemodialysis. Patients with pre-existing renal disease were excluded from the analysis which was concerned only with those patients with ARF caused by a demonstrable complication of pregnancy. These criteria also excluded those with severe obstetric complications in whom renal impairment was minor or transitory and required no specific therapy.

Patient details were stored on an IBM PC with 360 kbyte Ramdisk using a diagnostic index program (D. H. Marshall & J. H. Turney 1987, unpublished) which analyses age, survival, year of presentation, and long-term outcome of up to four diagnostic categories for each patient.

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Further statistical analyses were performed using the Oxstat (C) program.

Results

Demography

There were 142 patients (median age 27·9 years) with ARF occurring as a complication of pregnancy. ARF developed at all stages of pregnancy (Fig. 1), with peak incidence at or near term and a smaller peak earlier, related to abortions. Deaths were proportional to the incidence of ARF, the apparently greater mortality in the last trimester being related to the larger number of cases. There has been a dramatic decline in frequency of obstetric ARF over the past 31 years (Fig. 2). In the early years, obstetric cases comprised 20–35% of all ARF, 30–50% of patients aged 15–45 years, and 50–100% of all female patients. The proportion declined progressively during the 1960s with only sporadic cases thereafter.

Survival

Of the 142 patients, 30 died during the episode of ARF, giving a 1-year actuarial survival of 78·8% and a 5-year survival of 74·9% (Fig. 3). Of the later deaths, three patients died 1 to 3 years after being established on regular dialysis therapy for bilateral acute cortical necrosis (ACN). The facility for regular long-term dialysis therapy was not available before 1962. Mortality increased with increasing age (Fig. 4). Survival was not greatly different throughout the study period, and in all years the outcome of obstetric ARF was significantly better than for patients of the same age with ARF of all causes and much better than for ARF in all age groups (Table 1). Those who died differed from survivors in the duration of oliguria and the consequently greater number of haemodialyses required (Table 2), this presumably reflecting the worse prognosis of the more severely ill patients. There was no difference between survivors and those who died in the length of time between initial presentation and referral to Leeds (mean 4·7, SD 4·11 days for all patients).

Causes

Of the total cases 95·6% were due to abortion, obstetric (ante- and/or postpartum) haemorrhage, or pre-eclampsia and its complications (Table 3). This classification is necessarily arbitrary and is mainly derived from the retrospective analysis of often incomplete case-records. Figure 5 shows the varying proportion of causes according to year of presentation, and clearly shows the disappearance of abortions after 1969 and the progressive decline in importance of haemorrhage. Later, complicated pre-eclampsia and other causes of ARF predominate.

The clinical features of the main groups are summarized in Table 4. Patients with ARF consequent upon obstetric haemorrhage tended to be older, and were of greater parity ($P<0{\cdot}01$ *vs* other groups; *t*-test) with a large proportion (25%) of grand multiparae ($P<0{\cdot}03$ *vs* other groups; χ^2-test). They had a significantly ($P<0{\cdot}05$) lower rate of hospital births than the pre-eclampsia group. Antepartum haemorrhage differed from postpartum haemorrhage only in duration of gestation (mean 34·25, SD 3·86 *vs* 37·23, SD 3·65 weeks, $P<0{\cdot}02$). Most (70%) cases of ACN occurred with antepartum haemorrhage, which in part accounts for the poorer survival of this group.

The problems associated with the analysis of records up to 30 years old are illustrated by the difficulty in identifying definite placental abruption. In 14 cases there was incontrovertible evidence of abruption, survival being 71·4% with 21·4% of patients developing ACN. Abruption might be inferred in a further 21 patients with both haemorrhage and pre-eclampsia, who thus form an overlap between the groups. These patients did not differ from the haemorrhage group but were of greater parity than the pre-eclamptic patients (mean 2·95, SD 2·97 *vs* 1·82, SD 1·43; $P<0{\cdot}05$). The prognosis of this overlap group was good, with 81·3% 1-year survival.

The patients in whom pre-eclampsia was the main aetiological factor were younger and of lower parity, although with a lower than expected proportion (61%) of primigravidae. They presented earlier in pregnancy, reflecting the severity of early pre-eclampsia, but more were delivered in hospital. Fetal mortality in both the eclamptic and the haemorrhagic groups was depressingly high (76% and 71% respectively).

Patients with illegal abortions were older and of greater parity than might be expected. Perhaps the most surprising feature was the good prognosis (Table 3), particularly in view of the sinister reputation of septic criminal abortions,

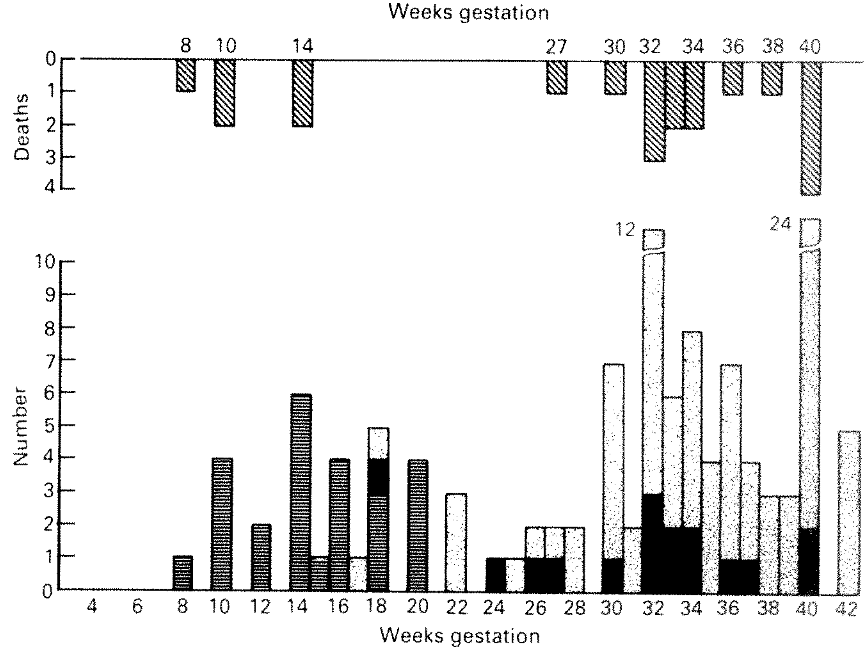

Fig. 1. Occurrence of obstetric acute renal failure (ARF) by week of gestation. ░, Obstetric ARF excluding; ■, acute cortical necrosis; ▤, abortion; ▨, deaths.

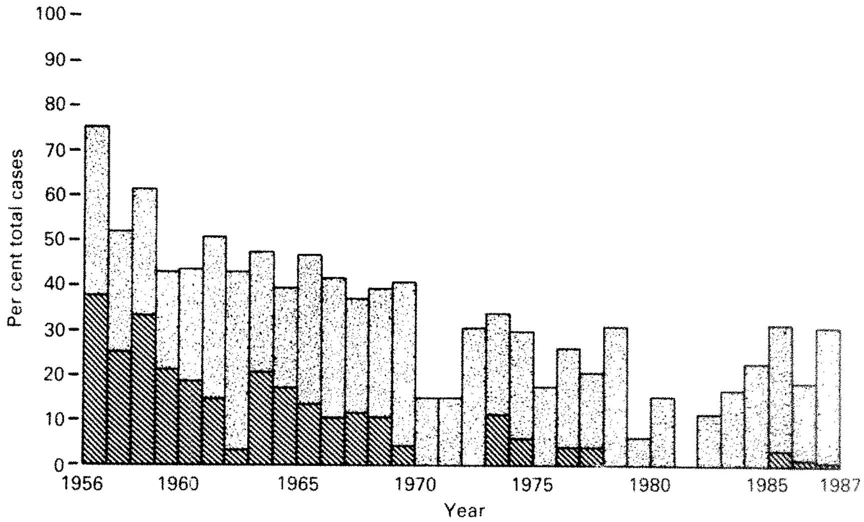

Fig. 2. Acute renal failure 1956–1987. ▨, Per cent total cases due to obstetric causes; ░, per cent total cases aged 15–45 years.

especially when associated with clostridial infection. In fact, although documented *Clostridium welchii* infection had a worse prognosis (30% mortality), only a minority (25%) of patients had proven infection with this organism; the remainder had a variety of other bacterial infections or no documented positive cultures (53%).

The mode of procuring abortion was poorly documented but included all the usual methods. Douches with detergents and other chemicals appeared common and may in part explain the low frequency of proven uterine infection, as chemical abortifacients may induce ARF directly by haemolysis (Janovski *et al.* 1963).

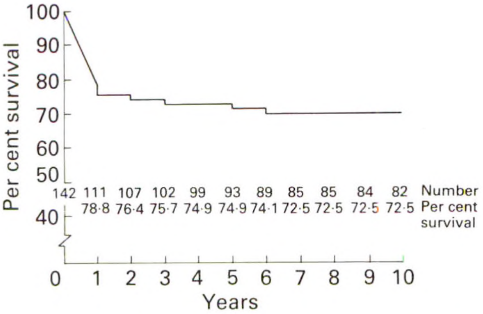

Fig. 3. Life-table analysis of survival following obstetric-related acute renal failure.

Of the patients with rarer causes of ARF (Table 5), six probably or definitely had acute fatty liver of pregnancy (AFLP). Some cases occurred before the condition had been fully described but retrospectively fulfill the clinical and laboratory criteria (Kaplan 1985). Similarly, six of the seven cases of idiopathic acute renal failure of pregnancy (Hayslett 1985) were diagnosed retrospectively. Both AFLP and idiopathic ARF carried a poor prognosis and have become major causes of uraemic emergencies in pregnancy in later years. ARF definitely due to acute pyelonephritis had a good prognosis. In only two patients, both from the 1950s, were mismatched blood transfusions definitely implicated as the main cause (Barry & Crosby 1963), but in other patients with obstetric haemorrhage there was evidence that mismatched blood or transfusion reactions contributed at least in part to the subsequent development of ARF.

Acute cortical necrosis

As obstetric ARF is the 'classic' cause of ACN, this deserves separate analysis. For the purposes of this study, the diagnosis of ACN has been accepted only if based on histological or radiological evidence in patients failing to recover renal function after a prolonged period or who developed severe chronic renal failure as a direct consequence of the obstetric ARF (Donohoe 1983). Overall, 18 patients (12·7%) fulfilled these strict criteria, which is probably an underestimate of the incidence of ACN (Fig. 1).

Not unexpectedly, survival with ACN was poor, being 29·4% at 1 year and 6% at 5 years (Fig. 6). In fact, exclusion of ACN results in a significant improvement in the overall survival for obstetric ARF, with 1-year survival improving from 78·6% to 85·8% and 5-year survival from 72·5% to 85·0% (Table 6). ACN obviously resulted in prolonged oliguria and consequently more haemodialyses (Table 2). Patients aged 30–45 years had a worse prognosis than younger individuals (12·5% *vs* 44·4% 1-year survival). Those in whom haemorrhage was the cause had a worse immediate prognosis than with pre-eclampsia (14·3% *vs* 36·4% 1-year survival). This suggests that severe pre-eclampsia resulted in more cases of partial ACN with consequent survival from the acute uraemic episode and death occurring later from progressive chronic renal failure. Three patients with ACN were maintained on regular dialysis therapy (in 1963 and 1965) and two patients received cadaveric renal allografts during the initial acute illness. Unfortunately, neither transplant, performed in 1959 and 1963 respectively, was successful, largely because of the poor clinical condition of the recipients. No cases of ACN were recorded after 1966.

Long-term follow-up

Known survivors are shown in Table 7; of these, 52 had normal renal function as judged by blood biochemistry 1 to 31 years after recovery from the episode of ARF. Eleven patients later had a total of 17 successful, uneventful pregnancies; nine underwent therapeutic termination of pregnancy (none because of renal disease); five were sterilized and eight had hysterectomies up to 15 years after the episode of ARF. Three patients died of malignancy 2, 5 and 5 years later: carcinoma of thyroid age 31 years, cervix age 42 years, and breast age 41 years. A further patient died of unknown causes after 11 years. Four

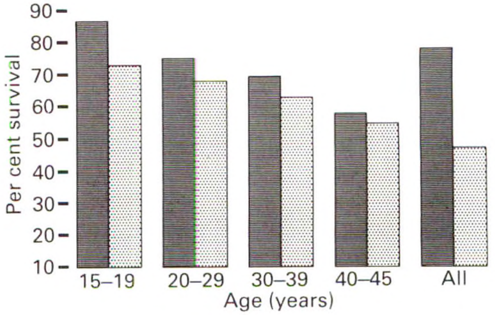

Fig. 4. One-year survival (%) (by age at presentation) of obstetric acute renal failure (▤), compared with acute renal failure from all causes (░).

Table 1. Numbers, deaths and 1-year actuarial survival of obstetric ARF, all patients with ARF aged 15–45 years, and all patients with ARF by year of presentation

	Obstetric ARF			ARF age 15–45 years			All ARF		
Years	*n*	D	Surv.	*n*	D	Surv.	*n*	D	Surv.
1956–59	53	13	75·2	107	40	61·0	209	103	47.4
1960–64	53	10	81·1	149	51	64·2	360	175	48·9
1965–69	25	4	84·0	96	34	63·4	225	112	47·9
1970–87	11	3	72·7	121	39	67·8	512	276	44·9
1956–87	142	30	78·8	479	166	64·3	1347	679	47·6

ARF, Acute renal failure; D, deaths; Surv., percentage survival at 1 year.

Table 2. Duration of oliguria and number of haemodialyses in all obstetric patients and those with acute cortical necrosis (ACN)

	Deaths		Survivors	
	Dialysis sessions	Oliguria (days)	Dialysis sessions	Oliguria (days)
All obstetric ARF	2·48 (1·5)*	26·14 (14·21)**	1·17 (1·28)	11·46 (8·34)
ACN	2·71 (2·09)†	27·67 (13·12)‡		

* $P<0{\cdot}0001$ deaths *vs* survivors; ** $P<0{\cdot}00001$ deaths *vs* survivors; † $P<0{\cdot}05$ ACN *vs* all obstetric; ‡ $P<0{\cdot}00001$ ACN *vs* all obstetric.
Results are mean (SD) values.

patients subsequently became hypertensive but with normal renal function, and one developed mild congestive cardiac failure. One patient has slowly progressive chronic renal failure (serum creatinine 370 μmol/l) 27 years after clinical recovery from the episode of ARF, following which renal function never returned entirely to normal. A further patient died of chronic renal failure after 17 years, but the relation to the episode of obstetric ARF is unclear.

Discussion

This series of severe obstetric acute renal failure treated by dialysis at a single centre confirms that obstetric ARF is now uncommon in the UK (Beaman *et al.* 1987). The disappearance of illegal abortions after the 1968 Abortion Act removed about one-third of cases. Improvement in antenatal care with the effective management of complicated pregnancies, the facility for safe early elective delivery when indicated, the improvement in resuscitation of obstetric haemorrhage, and the increased proportion of hospital births have all contributed to the prevention of this devastating complication of pregnancy. Thus, most of the cases reported here would have been preventable by modern obstetric practice. The impact of all these factors is shown by the radical change in incidence of obstetric ARF in Britain, from an estimated 1 per 5000 pregnancies in the 1950s (Kerr & Elliott 1963) to no cases observed in approximately 30 000 deliveries at The General Infirmary at Leeds from 1980 to 1987, despite its being a referral centre for complicated pregnancies. Nevertheless, ARF remains a major cause of

Table 3. Obstetric acute renal failure: actuarial 1- and 5-year survival of major clinical subgroups

		Deaths		Per cent survival	
Group	*n*	1-year	5-years	1-year	5-years
Abortion	35	6	6	82·9	82·9
Haemorrhage	48	10	11	79·2	77·0
Pre-eclampsia	69	16	21	76·8	68·6
Total*	142	30	38	78·8	74·9

* Numbers greater than total number of patients with obstetric ARF because of overlap between categories.

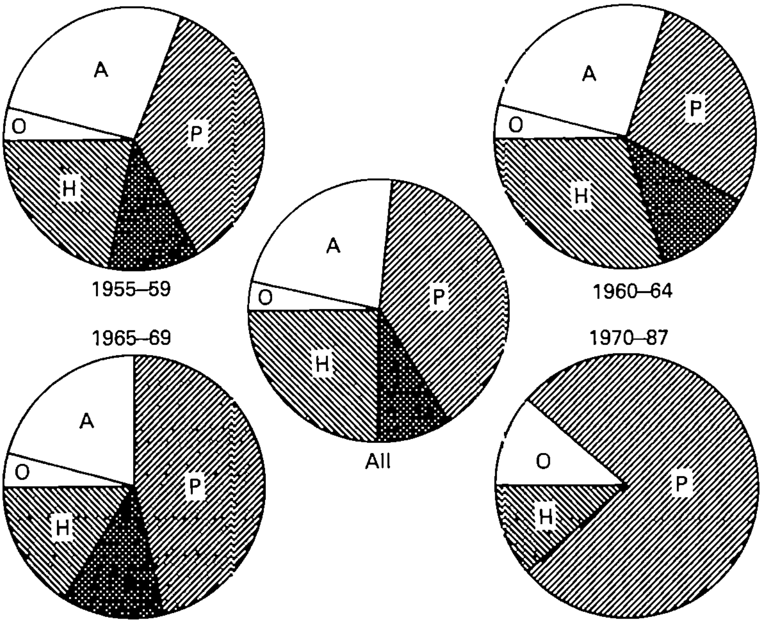

Fig. 5. Proportion of obstetric acute renal failure, according to major cause, grouped by year of presentation. A, Abortion; H, obstetric haemorrhage; P, pre-eclampsia, O, other causes.

maternal death in some countries (Chugh *et al.* 1976, 1983; Adu *et al.* 1976), where obstetric causes contribute about 20% of all cases of ARF or about 50% of female cases. It is the Leeds experience that ARF now only occurs in pregnancies with unusual complications such as acute fatty liver or idiopathic postpartum ARF. These patients have severe disorders with multi-organ involvement and consequently carry a relatively poor prognosis.

It is now universally accepted that the only effective treatment of an acute uraemic illness is replacement of renal function by dialysis. However, this was far from the case 30 years ago: 'There is thoughtful medical opinion that this type of therapy (dialysis) is of little value' (Knapp & Hellman 1959). Consequently the mortality of conservatively treated obstetric ARF was variously reported at between 45% and 90% (Bull *et al.* 1950; Ober *et al.* 1956; Kerr & Elliott 1963; Chugh *et al.* 1976) which contrasts sharply with the results in this series of cases treated by haemodialysis. It would appear (Table 2) that dialysis during the anuric phase was performed relatively infrequently by the standards of modern practice. This resulted from two factors that obtained in the earlier years of dialysis treatment. The introduction of norethandrolone (Blagg & Parsons 1960) greatly reduced the metabolic response in patients with ARF late in pregnancy (rise of blood urea reduced by up to 70%), and the awesome ability

Table 4. Obstetric acute renal failure: comparison of clinical features of major subgroups

Group	*n*	Median age (years)	Parity	Gestation (weeks)	Stillbirths (%)	Hospital births (%)
Abortion	35	29·4	2·6 (0–5)	14·5 (6–24)	—	—
Haemorrhage	48	30·2	4·7 (0–11)	35·5 (27–44)	71	21
Pre-eclampsia	69	27·8	1·8 (0–6)	34·4 (18–40)	76	59

Table 5. Uncommon causes of obstetric acute renal failure

	n	Deaths	Per cent survival
Acute fatty liver	6	2	66·7
Acute pyelonephritis	4	0	100
Idiopathic ARF of pregnancy	7	3	57·1
Mismatched transfusion	2	0	100
Neurosurgery (post-eclampsia)	1	1	0
Hyperemesis gravidarum	1	0	100

of the Kolff–Brigham–Necker–Leeds rotating artificial kidney (Parsons *et al.* 1961) to increase clearance rates over other dialysers led to a significant prolongation of time between dialyses.

The apparently long time between presentation and referral resulted from a variety of factors. In the earlier period of the study, it was accepted practice to manage ARF conservatively by means of 'Bull's regimen' (Bull *et al.* 1950), as a consequence of which many patients were profoundly uraemic, hyperkalaemic, and acidotic by the time of referral. A significant number had uraemic coma or fits before transfer and a high proportion required emergency dialysis. The value of dialytic therapy had yet to be established and as a result there were few dialysis centres in the UK. The gradual establishment of other renal units during the 1960s necessarily altered the pattern of referral. In the present series, 48·3% of patients were transferred less than 25 miles while 10·1% were referred from hospitals more than 100 miles from Leeds. The difficulties associated with the inter-hospital transfer of very sick patients were considerable. Many were transferred by train, for example on the overnight expresses from Scotland.

It is now accepted that the oliguric phase of ARF may occasionally extend to many weeks with eventual recovery of renal function (Finn 1983). In the early days of dialysis, technical problems with vascular access and pressure on limited facilities meant that repeated frequent dialyses over a prolonged period were not possible. Although the oliguric phase was relatively short in the majority of patients (Table 2), some with prolonged oliguria were classified as 'irreversible' but in only some of these was there compelling evidence of ACN. The impact of the relatively few cases of ACN on the overall mortality (Table 5) underlines the fact that obstetric ARF has a good prognosis when compared with ARF in general (Table 1), especially when analysis is confined to cases of 'reversible ARF'.

The good outcome of obstetric ARF is presumably related to a combination of a self-limiting precipitating cause and a young and otherwise healthy population. There is evidence from the present series that, even in this young population, increasing age adversely affected outcome. Survival has not improved since the establishment of haemodialysis in Leeds in 1956, and has in fact declined a little in later years, reflecting the greater severity and multi-organ involvement of recent cases. In contrast to other series of ARF (Stott *et al.* 1972; Kennedy *et al.* 1973; Wheeler *et al.* 1986; Beaman *et al.* 1987), overwhelming sepsis was uncommon in this study and contributed little to the overall mortality.

Most survivors of the acute uraemic episode have an excellent long-term prognosis for both renal and patient survival. We can find no evi-

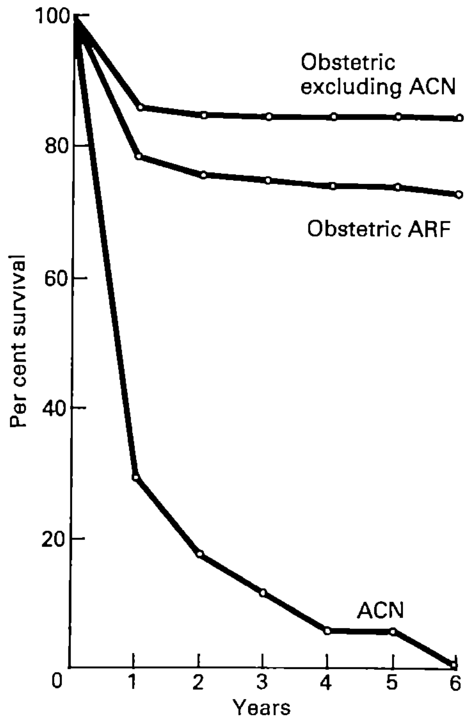

Fig. 6. Percentage survival of bilateral acute cortical necrosis (ACN) compared with all obstetric acute renal failure, with and without the inclusion of ACN cases.

Table 6. One- and 5-year actuarial survival (%) of patients with obstetric acute renal failure, including and excluding those with acute cortical necrosis

	All obstetric ARF		Obstetric ARF excluding ACN	
Year	1-year	5-year	1-year	5-year
1956–59	75·2	69·0	86·2	83·8
1960–64	81·1	75·3	89·0	89·0
1965–69	84·0	79·2	86·4	86·4
1956–87	78·8	72·5	85·8	85·0

ARF, Acute renal failure; ACN, acute cortical necrosis.

dence of later development of chronic renal failure after apparently full recovery of function (Finn 1983). Chronic renal failure only developed after complete or partial ACN, the majority of whom died during the initial illness or from end-stage renal failure within a short period. We have no cases of later improvement of function in patients left with significant renal impairment after the acute illness, as has been occasionally reported (Donohoe 1983), and feel that renal recovery is extremely improbable in patients with incontrovertible ACN. There seems no simple explanation of why obstetric patients are relatively prone to develop ACN or why the condition has virtually disappeared. However, in pregnancy some or all of the following pathogenetic mechanisms may coincide (Andreucci 1985): hypovolaemia due to blood loss and contracted plasma volume; apparent inability of the kidneys during hypertensive pregnancy to compensate fully for additional factors; pre-eclampsia; disseminated intravascular coagulation; and sepsis. The combination of pregnancy-induced hypertension, reduced plasma volume and intrauterine haemorrhage ('concealed accidental haemorrhage') appears to induce a profound vasomotor nephropathy with consequent shut-down of renal cortical blood flow, formerly referred to as the 'uterorenal reflex'.

Table 7. Survivors of obstetric acute renal failure with known normal renal function

	Year of follow-up					
	1	5	10	15	20	25
Number	102	93	82	74	61	38

The present series is comparable with other studies of obstetric ARF (Pertuiset & Grunfeld 1987), but the large numbers, longer time-scale and consideration of only those patients with the severest ARF provides some insights relevant to modern practice, particularly the value of prevention of ARF by improved standards of management and resuscitation or by legislation leading to prevention of criminal abortion.

Acknowledgments

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Abdominal pain of unknown aetiology in pregnancy

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Summary. The outcome of 140 pregnancies complicated by unexplained abdominal pain was compared with that in a comparison group of 280 women who gave birth at the same time. The two groups were comparable for maternal age and parity but the study group contained a significantly higher proportion of smokers, unmarried women, and women whose partners were unemployed ($P<0{\cdot}001$). All the pregnancies resulted in livebirths. There were no statistically significant differences in birthweight, gestational age at delivery or mode of delivery between the two groups.

A large number of antenatal patients are admitted with or following an episode of lower abdominal pain. Whilst for many patients a diagnosis such as urinary tract infection, the onset of labour, acute appendicitis or placental abruption can be made, in a substantial number there is no diagnosis despite investigations (Tomkinson 1970).

Many studies have examined fetal morbidity and mortality in pregnancies where a cause for abdominal pain can be discerned (Ellsbury 1986; Hurd *et al.* 1983) but in pregnancies where no cause is found, little is known about the subsequent outcome. Rayburn *et al.* (1981) suggested that in about 65% of the pregnancies that have a poor outcome, this could not have been predicted.

This study aimed to examine the hypothesis that abdominal pain of unknown aetiology in pregnancy should be regarded as an antenatal risk factor for a poor outcome of pregnancy assessed in terms of birthweight, length of gestation and mode of delivery.

A group of women with abdominal pain was compared with a group of women without abdominal pain in respect of five variables known to be associated with these outcomes, namely birthweight, maternal age, parity, proportion of smokers, marital status and employment status of partners.

Subjects and methods

Women eligible for the study were patients admitted with lower abdominal pain at 28–37 weeks gestation to University Hospital, Nottingham, over a period of 12 months. The women were investigated with ultrasound, cardiotocography (CTG), urine culture and placental function tests.

Exclusions

Only patients with a gestational age over 28 weeks were included in the study because if abdominal pain was proven to be a significant risk factor, accelerated delivery could be contemplated. Furthermore, at earlier gestations the investigations above are inappropriate. The upper limit of gestational age was set at 37 weeks in an effort to exclude patients in spurious or early labour. For the same reason women delivered within 1 week from the onset of the abdominal pain were excluded from the study, this applied to 21 women.

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Six patients with urinary or bowel symptoms were excluded, four had significant urinary symptoms, frequency and dysuria, and two had diarrhoea. A further 13 patients were excluded because they had abnormal findings: on ultrasound (n=4), CTG (n=2), urine culture (n=6) or serum oestriol assay (n=1).

Study group

A total of 140 women fulfilled the entry criteria and formed the study group, they constituted approximately 14% of the total number of antenatal patients admitted between 28 and 37 weeks gestation. All the 140 women had normal ultrasound scans with fetal biparietal diameter and abdominal circumference measurements between the 5th and 95th centiles. All of them had one or more CTG recordings which were considered normal by a member of the medical staff. In 129 women (92%) mid-stream urine specimens were cultured, none showed significant infection. Serum oestriol was estimated in 78 women (56%), all values were within the normal range for gestational age.

Comparison group

A comparison group was constructed by selecting the deliveries which succeeded and preceded each delivery entered in the study group, giving a comparison group twice as large as the study group.

Statistical analysis

In analysing the results the standard error of the difference between two means was used when comparing mean maternal age, mean gestational age at delivery and mean birthweights, and the 95% confidence intervals (CI) were also calculated. The χ^2-test was used to compare the proportions of primigravidae, smokers, unmarried women, women whose partners were unemployed, and the mode of delivery between the two groups.

Results

Of the 140 patients in the study group, the mean gestational age on first admission was 30·5 weeks; 21 of them (15%) were admitted again later in the pregnancy between 1 and 9 times with lower abdominal pain. Again, no diagnosis was made.

Table 1 compares the characteristics of the women in the study group with those in the comparison group. There was no significant difference in mean maternal age between the two groups (P>0·1, 95% CI −0·2 to 1·0) and there was no significant difference in the proportion of primigravidae (P>0·1). A significantly higher proportion of the women in the study group were smokers (P<0·01), single (P<0·01) and had partners who were unemployed (P<0·001).

Outcome of pregnancies

All the pregnancies in both groups resulted in live infants. Table 2 compares the outcome in the two groups. Using standard error of the difference between two means, and the 95% CI to compare mean birthweights showed no significant difference (difference between means 0·06 kg, SE difference 0·035, P>0·05, 95% CI −0·01 kg to 0·13 kg). In all other comparisons no significant differences were found (P>0·1) (Table 2).

Discussion

This study has identified no statistically significant differences in the outcome of pregnancy

Table 1. Characteristics of the two groups

Variable	Study group (n=140)	Comparison group (n=280)	Relative risk	P
Mean maternal age (years)	25·4	25·9		NS
Primigravidae	57 (40·7%)	118 (42·1%)	0·97	NS
Smokers	67 (47·9%)	90 (32·1%)	1·49	<0·01
Single women	43 (30·7%)	52 (18·5%)	1·66	<0·01
Women with unemployed partners	49 (35·0%)	44 (15·7%)	2·23	<0·001

Results are numbers of women with percentages in parenthesis.

Table 2. Outcome of pregnancies in the two groups

Variable	Study group (n=140)	Comparison group (n=280)	Relative risk	P
Gestational age at delivery (weeks)	38·8 (32–42)	39·1 (34–42)		NS
Birthweight (kg)	3·28 (1·74–4·45)	3·34 (2·02–4·51)		NS
Mode of delivery				
Normal vaginal	108 (77·1%)	205 (73·2)	1·05	NS
Instrumental	18 (12·9%)	45 (16·0)	0·81	NS
Caesarean section	14 (10·0%)	30 (10·7)	0·93	NS

Results are mean (range) or n (%) values as appropriate.

between a group of women with unexplained abdominal pain and a comparison group of women delivered at the same time. These findings suggest that episodes of lower abdominal pain where investigations yield no diagnosis ought not to influence subsequent management of the pregnancy.

The characteristics of the two groups differed in that the study group contained a higher proportion of smokers, single women and women whose partners were unemployed. All these characteristics have been associated with reduced birthweight (Cardozo *et al.* 1982; Barron & Thompson 1983) and might have been expected to result in a relatively poorer outcome in the study group. The fact that there were no statistically significant differences in outcome between the two groups further refutes the hypothesis that abdominal pain in pregnancy is an antenatal risk factor.

The comparatively high proportion of single women, smokers and women whose partners are unemployed in the study group suggests there may be socio-economic factors influencing admission of pregnant women with unexplained lower abdominal pain. It is possible that in some women social factors lowered the pain threshold for presenting at hospital. Single women without the support of a husband may have felt a greater need for medical attention, or more anxiety regarding the eventual outcome of the pregnancy.

However, the composition of our study group may contain an important bias since by definition it included only women who had 'normal' ultrasound scans, CTG tracings and serum oestriol values within the normal range (in the 78 women investigated). If these criteria were not met the patient was excluded from the study. No similar restrictions were placed on the comparison group. Furthermore, after an admission with lower abdominal pain, patients in the study group may have received more antenatal monitoring and more frequent antenatal clinic visits.

The problem remains as to the underlying cause of the pain in our study group. Many of the organic causes of abdominal pain such as pyelonephritis are, as a rule, easily recognized (Chamberlain 1969). Round ligament pain is a recognized condition which Bourne (1984) described as an aching, dragging pain, rarely necessitating pain-killing drugs, often more severe on the right side of the abdomen, just lateral to the uterus and occurring until about 31 weeks gestation. Pain in the hypochondrium may be due to pressure on the lower ribs caused by the enlarged uterus (Tomkinson 1970). Although all our patients had an ultrasound scan one should not assume that a 'normal' scan excludes placental abruption (Cohen *et al.* 1980). The reliability of ultrasound scanning for this diagnosis is poor and only a positive diagnosis should be taken into account (Jeanty & Romero 1984). Possibly a small placental separation is a cause of the abdominal pain, although in none of our 140 patients was any placental abruption noted later in the pregnancy or at delivery.

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Umbilical artery velocity waveforms: poor association with small-for-gestational-age babies

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Summary. A total of 205 high-risk pregnancies was studied using continuous wave Doppler ultrasound examination of the umbilical artery to investigate the ability of the test to detect small-for-gestational-age (SGA) infants. The waveforms were analysed by calculating a ratio of the peak systolic to end diastolic frequency (A/B ratio). An A/B ratio >95th centile from our derived normal values was classified as abnormal. Three outcome variables were examined: birthweight for gestational age, the standard deviation birthweight score and the ponderal index. Although of the 56 pregnancies with an abnormal Doppler result 34 (61%) were associated with a SGA infant, only 41% of all the SGA infants had an abnormal Doppler result. Alternative measures of growth, the ponderal index and the SD birthweight score, showed that on average the babies in the Doppler abnormal group were smaller than those in the Doppler normal group, but the overlap between the normal and abnormal groups was large. Therefore although Doppler ultrasound appears to identify groups of smaller babies, it does not identify individual pregnancies where the baby will be small at birth.

An important part of prenatal care is the detection of intrauterine growth retardation (IUGR) as these babies are at higher risk of complications *in utero* (Tejani & Mann 1977), during labour (Low *et al.* 1972; Lin *et al.* 1980), and in the neonatal period (Battaglia 1970; Neligan *et al.* 1976; Fitzhardinge *et al.* 1978). Infants who have suffered severe IUGR may never achieve their full potential (Taylor 1984, 1988).

Several reports have claimed that analysis of the waveforms obtained from the fetal circulation using Doppler ultrasound is a highly specific method of identifying babies with IUGR (McCallum *et al.* 1978; Reuwer *et al.* 1984; Erskine & Ritchie 1985; Trudinger *et al.* 1985*a*; Fleischer *et al.* 1985). The validity of these claims was investigated in this study.

Patients and methods

The study included 205 women with high-risk pregnancies who were admitted to the antenatal ward. The main indications for admission were suspected small-for-gestational-age in 89 women, hypertension in 70, antepartum haemorrhage in 19, diabetes in 14, threatened preterm labour in six, and miscellaneous problems in seven women. Gestational age had been confirmed in all women by a dating scan in the second trimester. All women had fetal umbilical artery flow velocity waveforms recorded within 7 days of delivery, and informed consent was obtained before the investigation. All the

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recordings were performed and analysed by one person (J.D.), and in each case the clinician was unaware of the result.

The signals from the umbilical artery were obtained using a 4-MHz hand-held Sonicaid continuous wave ultrasound probe. With the women lying comfortably in a semi-recumbent position to avoid aorto-caval compression, the probe was positioned on the abdomen until the best quality Doppler signals were obtained. The signals were stored on magnetic tape using a Phillips stereo tape recorder and played back through an Angioscan III for spectral analysis. A permanent record was made using an on-line Epson FX80 printer. The sonograms obtained were analysed by determining the ratio of peak systolic (A) to end diastolic (B) frequency (A/B ratio) (Stuart *et al.* 1980). To establish the reference graph of normal values, 50 healthy women with uncomplicated pregnancies were studied longitudinally on seven occasions in the second half of pregnancy. All the babies were born vaginally and had birthweights above the 10th centile after correction for maternal height and weight, infant's sex and birth order (Altman & Coles 1980*a*). For each gestation studied (19, 24, 28, 30, 34, and 40 weeks), the median, 5th, 10th, 90th and 95th centiles were calculated. The A/B ratios obtained from the high-risk pregnancies were plotted on the reference graph (Fig. 1) and an abnormal Doppler result was defined as an A/B ratio above the 95th centile.

Three indices of fetal growth were studied: birthweight for gestation, standard deviation birthweight score and ponderal index.

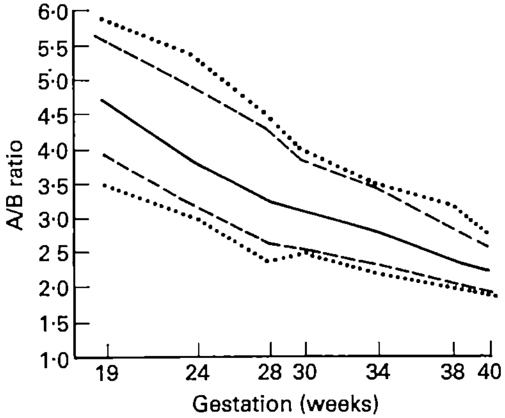

Fig. 1. Reference values of A/B ratio plotted against gestation, derived from a longitudinal study of 50 healthy women with normal pregnancy. —, Median, ---, 90th and 10th centiles; ....., 5th and 95th centiles.

Small-for-gestational-age (SGA) was defined as a birthweight <10th centile after correction for maternal height and weight, infant sex and birth order (Altman & Coles 1980*a*).

To avoid the possible confounding effects of gestational age at birth, infant sex and birth order, maternal height and weight, birthweight was expressed as the number of standard deviations (SD) above or below the mean using the computational formulae derived by Altman & Coles (1980*b*) (standard deviation birthweight score).

Ponderal index was calculated as an index of body mass according to the formula: birthweight (g)×100/length^3 (cm).

The following measures of clinical outcome of the SGA babies were studied: gestation at delivery, occurrence of operative delivery, late fetal heart rate decelerations in labour (as defined by Hon 1962), and admission to the special care baby unit (SCBU).

Differences between groups were analysed using χ^2- and t-tests.

Results

Of the 205 women with high-risk pregnancies, 82 (40%) gave birth to SGA babies. There were 56 pregnancies with abnormal Doppler findings (A/B ratio >95th centile) and the other 149 had normal Doppler findings. The proportion of SGA babies in the group with abnormal Doppler findings was 61% (34 of 56) which was significantly greater than the proportion of SGA babies in the group with normal Doppler findings (32%, 48 of 149, $P<0·001$). However, in terms of actual numbers more SGA infants had normal Doppler findings (48 of 82; 59%) than abnormal Doppler findings (34 of 82; 41%).

No SD birthweight score could be calculated for four women with high-risk pregnancies who were delivered before 33 weeks gestation which is outside the limits provided by Altman & Coles (1980*b*). For each of the other 201 high-risk pregnancies a SD birthweight score was calculated (Fig. 2). The SD score of the Doppler abnormal group (mean=−1·44, SD=1·19, $n=55$) was significantly lower than that in the Doppler normal group (mean=−0·81, SD=1·0, $n=146$) ($t=3·23$; $P<0·01$). However, as can be seen from Fig. 2, the two groups overlap considerably.

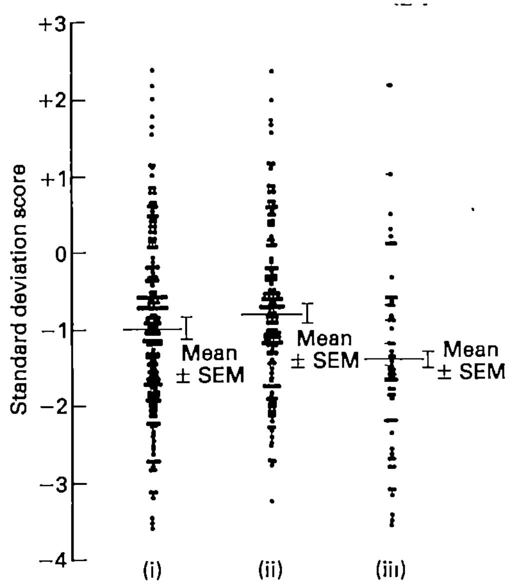

Fig. 2. Standard deviation birthweight score for 201 high-risk pregnancies The individual results are shown in three groups with the mean (±SEM): (i) all 201 pregnancies; (ii) the 146 pregnancies with normal Doppler findings; and (iii) the 55 pregnancies with abnormal Doppler findings.

In 21 pregnancies the length of the baby was not recorded so that a ponderal index could not be calculated. The individual results of ponderal index are shown in Fig. 3 categorized according to the Doppler findings. The difference between the group with normal Doppler findings (mean 2·48, SD=0·28, n=135) and the group with abnormal Doppler findings (mean 2·27, SD=0·39, n=49) was statistically significant (t=4·03; P<0·001), but as in the case of the SD birthweight score, there is considerable overlap.

Eighty-two infants were SGA at birth. The mean gestational age at delivery in the Doppler abnormal group (36·7 weeks, range 30–40) was lower than that in the Doppler normal group (38·2 weeks, range 32–41) but the difference was not statistically significant.

The rate of operative delivery was higher in the Doppler abnormal group, 70·5% *vs* 42% (P<0·01). Forty-one of the 149 women with normal Doppler results laboured, and 5 (12%) of them developed late fetal heart decelerations in labour. Of the 56 women with abnormal Doppler results 24 were allowed to labour and 13 (54%) of them showed late fetal heart rate decelerations. This difference is statistically significant, P<0·001. The proportion of the SGA babies admitted to the SCBU was 56% in the Doppler abnormal group (18 out of 32 SGA livebirths) and 26% in the Doppler normal group (12 out of 47 SGA livebirths) (P<0·01). There was one intrauterine death in the Doppler normal group which was due to placental abruption and two intrauterine deaths in the Doppler abnormal group, one death was associated with IUGR and one was due to placental abruption.

Discussion

Because of the high morbidity and mortality associated with poor fetal growth (Tejani & Mann 1977; Low *et al.* 1972; Lin *et al.* 1980; Battaglia 1970; Neligan *et al.* 1976; Fitzhardinge *et al.* 1978) it is important to detect this condition antenatally. The differentiation between suboptimal fetal growth due to intrauterine growth restraints and adequate growth of a genetically small infant is difficult. The terminology used throughout this study is SGA, meaning any baby born with a birthweight below the 10th centile after appropriate correction (Altman & Coles 1980*a*). The decision to use the lower 10th centile of birthweight as a definition of SGA is entirely arbitrary, but no cut-off level guarantees that all cases of true IUGR will be included

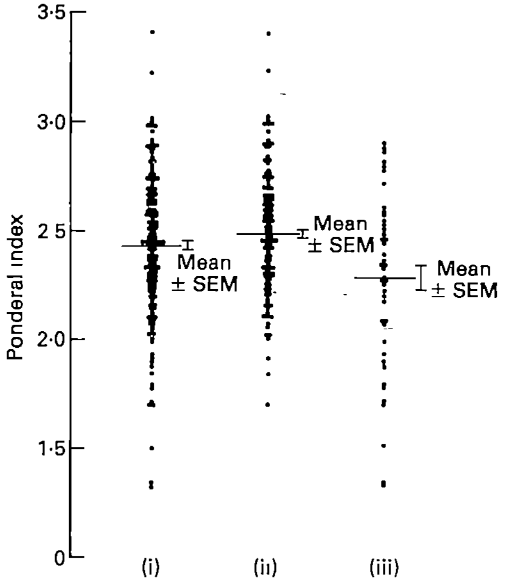

Fig. 3. Ponderal index in 184 high-risk pregnancies. The individual results are shown in three groups with the mean (±SEM): (i) all 184 pregnancies; (ii) the 135 pregnancies with normal Doppler findings; and (iii) the 49 pregnancies with abnormal Doppler findings.

(Keirse 1984) and it will include a large number of infants whose growth has not been impaired (Bakketeig *et al.* 1979).

In this study, although a significantly higher proportion of babies in the Doppler abnormal group were SGA (61%) compared with the Doppler normal group (32%), in terms of actual numbers more SGA infants had normal Doppler results (59%) than abnormal Doppler (41%). Assuming that the placental resistance of a genetically small infant with no growth constraints is normal, Doppler flow velocity waveforms could be expected to be normal, and, conversely, the fetus with suboptimal growth due to placental pathology might be expected to have abnormal Doppler flow velocity waveforms. As it is unlikely that all SGA infants studied were nutritionally deprived due to placental problems the results obtained in this study are to be expected.

These results contrast markedly with most other published work on the detection of small babies using Doppler, where Reuwer *et al.* (1984), Fleischer *et al.* (1985), Trudinger *et al.* (1985*a*) and Erskine & Ritchie 1985) noted abnormal Doppler findings in 19 out of 20, 18 out of 23, 32 out of 43 and 9 out of 9 growth-retarded infants, respectively. The ability to predict and detect such a high proportion of small babies is surprising in view of the heterogeneous nature of SGA infants. Our study does not confirm the claim of these studies that Doppler identifies most small babies. Our results may differ because of patient selection, but in our high-risk population with a 40% frequency of SGA most of the SGA babies had normal umbilical artery flow velocity waveform patterns. The reference graph of normal values was constructed from a population of healthy pregnant women who gave birth to infants with a birthweight above the 10th centile, therefore it cannot be argued that choosing the 95th centile as a cut-off level between normal and abnormal A/B ratios would only be expected to detect half of the SGA infants, defined as a birthweight <10th centile.

Another method of comparing birthweight both clinically and epidemiologically is to use the SD birthweight score which allows standardization for factors which might confound birthweight analysis. An alternative to using birthweight for comparing nutritional status of infants is to use a ponderal index. The Rohrer ponderal index, described by Miller & Hassanein (1971), was introduced over 60 years ago for assessing nutritional status. The mean SD birthweight score and ponderal index of the babies in the Doppler abnormal group was significantly lower than in the babies born in the Doppler normal group. This suggests that within a group of pregnancies suspected on clinical grounds to be 'high risk' an abnormal Doppler result can select a subgroup of pregnancies where the mean infant birthweight and body mass are significantly lower than in the babies with normal Doppler results. But the spread of results was wide and would be of little value in identifying an individual fetus at risk.

In contrast to other workers we have found that Doppler ultrasound examination of the umbilical artery has a poor association with fetal weight for gestation. Using other indices of growth, namely ponderal index and SD birthweight score, we have shown that although Doppler ultrasound appears to identify groups of smaller, leaner babies, it does not reliably identify individual pregnancies where the baby will be small. However, when SGA babies with normal Doppler results were compared with SGA babies with abnormal Doppler findings, the Doppler abnormal group were found to have a significantly increased rate of operative delivery, late FHR decelerations in labour, and increased admission to the SCBU. These results are in agreement with other reports (Trudinger *et al.* 1985*b*; Rochelson *et al.* 1987*a,b*). There was one intrauterine death in the group with normal Doppler findings, but it was related to placental abruption. Our findings would suggest that Doppler studies of the umbilical artery, rather than identifying all small babies *in utero*, may help in identifying a group of SGA infants at increased risk of intrapartum hypoxia.

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Evidence of redistribution of cardiac output in asymmetrical growth retardation

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Summary. Thirty-one fetuses with growth retardation were studied by Doppler estimation of the cardiac output from each side of the fetal heart. Asymmetrical growth retardation was diagnosed in 16 fetuses by a head to abdominal circumference ratio above the 95th centile. In the 15 fetuses with symmetrical growth retardation, the distribution of cardiac output was normal. The mean and maximum velocity of blood flow in the pulmonary artery and aorta were similar to values in normal fetuses, and there was a greater calculated output from the right heart than from the left. The right heart flow expressed as a percentage of the combined cardiac output was not statistically significantly different from that in normal fetuses. In contrast, all 16 fetuses with asymmetrical growth retardation had a higher mean and maximum velocity in the aorta than in the pulmonary artery. The calculated volume flow from each side of the heart showed a greater output from the left than the right heart in 15. The right heart flow expressed as a percentage of the combined cardiac output was statistically different from the value in normal fetuses. These findings are consistent with theories of the redistribution of fetal blood flow, where cerebral blood flow is preferentially 'spared'.

Many workers have studied intrauterine growth retardation using Doppler techniques to interrogate several different sites within the fetus. A quantitative and qualitative change in blood flow has been demonstrated in the descending aorta by Eik-Nes *et al.* (1980, 1984), Tonge *et al.* (1983, 1986), Griffin *et al.* (1984, 1985) and Jouppila & Kirkinen (1986). A reduction of venous return to the heart has also been suggested from the calculation of blood flow in the umbilical vein in the affected fetus (Gill *et al.* 1984; Jouppila & Kirkinen 1984*b*). Changes in flow velocity waveforms in the umbilical and uterine arteries have been found in growth-retarded fetuses (Schulman *et al.* 1984; Trudinger *et al.* 1985; Erskine & Ritchie 1985; Campbell *et al.* 1983). Alterations in blood flow patterns in the cerebral circulation in the 'head-spared' growth-retarded fetus have also been detected, indicating decreased resistance in the intracerebral vessels (Marsal *et al.* 1984; Wladimiroff *et al.* 1986).

In the normal fetus there is a higher output from the right heart than from the left heart. The pulmonary artery flow varies from 50 to 70% of the combined cardiac output with a mean of 58%

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(Allan *et al.* 1987). These results are similar to the findings of other workers (Reed *et al.* 1986; De-Smedt *et al.* 1987). We investigated a series of growth-retarded fetuses with Doppler ultrasound to assess the relative outputs of the two ventricles.

Subjects and methods

Comparison group

The data used for comparison with the growth-retarded fetuses were collected from 92 normal pregnancies referred for echocardiography or recruited as volunteers from the antenatal clinic at 18–40 weeks gestation. Postnatal follow-up confirmed a normal outcome in all pregnancies.

The study group included 31 women admitted to hospital because fetal growth retardation had been suspected on routine obstetric care. Their gestational age ranged from 20 to 39 weeks.

Intrauterine growth retardation was defined by a clinical discrepancy of >2 weeks combined with ultrasound findings of abdominal circumference measurement below the 10th centile (Campbell 1976) together with postnatal confirmation by a birthweight < the 10th centile for gestational age adjusted for sex and parity according to Thomson *et al.* (1968) in the first 14 babies but latterly adjusted also for maternal height and mid-term weight according to the criteria of Altman & Coles (1980)

The head and abdominal circumferences were measured and the ratio calculated. Asymmetrical growth retardation was diagnosed if the ratio was > the 95th centile (Campbell & Thoms 1977). A Hewlett-Packard 77020A phased array sector scanner with pulsed Doppler facility was used with a 3·5 or 5 MHz transducer. This allows an axial resolution of 1·0 and 0·7 mm, respectively. The velocity of blood flow was recorded in the aorta and pulmonary artery just above their origin from the heart. Flow calculations were made from the product of the area of the vessel and the mean temporal velocity of blood flow through each valve as described previously (Allan *et al.* 1987). Doppler flow was assessed in the umbilical artery as described previously (Al-Ghazali *et al.* 1987).

For the diameter measurement both intra- and inter-observer reproducibility was assessed. Real-time images of the aorta or pulmonary artery were displayed in 10 fetuses at between 32 and 37 weeks gestation four times for each fetus. The diameter measurement was recorded only when the beam was perpendicular to the vessel and the walls very clear. The internal diameter was measured at the level of the valve in diastole where a central echo of the closed valve was demonstrated. The same procedure was repeated on the same fetus after approximately 15 min. For inter-observer reproducibility the aorta and pulmonary artery were displayed in 10 fetuses, four times for each fetus. Two observers measured the vessel diameter on each image independently. The reproducibility of blood flow velocity measurements in the aorta and pulmonary artery was determined in 10 subjects. Three measurements were performed by the same examiner at intervals of 10–15 min. For each of the three measurements three beats were analysed and an instant mean velocity was measured.

Data analysis

Doppler and echocardiographic variables were plotted against gestational age and correlations were determined. A paired *t*-test was used to compare blood flow velocities in the aorta and pulmonary arteries obtained from the same patient in each group studied. An unpaired *t*-test was used to compare the same measurement in different patients.

Results

Normal fetuses

Table 1 shows that there was no significant difference between the mean velocity of blood flow in the aorta compared with that in the pulmonary artery [19·1 (SD 4·4) *vs* 18·4 (SD 3·5); P=0·2] but the maximum velocity was significantly greater in the aorta [77·0 (SD 14·9) *vs* 68·8 (SD 13·0); P<0·00001]. The ratio of right heart flow/combined cardiac output expressed as a percentage was unchanged throughout pregnancy (r=0·03), and was a mean of 57·9% (SD 7). The combined cardiac output in normal fetuses ranged from 150 ml/min at 18 weeks to 1200 ml/min at 40 weeks gestation. The flow per kilo ranged from 300 to 500 ml/kg/min (mean 408·7, SD 88·7) throughout pregnancy. The estimated fetal weight was derived from the fetal biparietal diameter and the abdominal circumference measurements (Jeanty & Romero 1983) or from

Table 1. Haemodynamic measurements in normal and growth-retarded fetuses

Group	*n*	Blood flow velocity: Aorta Maximum	Aorta Mean	Pulmonary artery Maximum	Pulmonary artery Mean
Normal	92	77·0 (14·9)	19·1 (4·4)	68·8 (13 0)	18·4 (3·5)
IUGR					
Symmetrical	15	72·6 (12·0)	17·5 (2·5)	68·7 (9·5)	18·3 (2·7)
Asymmetrical	16	75·1 (14·6)	19·0 (4·6)	55·6 (12·6)	13·8 (3·6)

IUGR, Intrauterine growth retardation
Results are mean (SD).

the birthweight in fetuses studied just before birth.

Abnormal fetuses

Symmetrical growth retardation. Of the 31 growth-retarded fetuses 15 were diagnosed as having symmetrical growth retardation. In 14 of these there was a normal distribution of blood flow, that is, a greater volume flow through the pulmonary valve than through the aortic valve; and in one fetus the flows were almost equal. All were within the normal range for cardiac flow ratios with no significant difference in mean or maximum velocities between the great arteries (Table 1) or in the ratio of right heart/combined cardiac output from normal. Twelve fetuses had a combined cardiac output around the low normal range for the gestational age, which can be accounted for by the smaller vessel size in these small fetuses, with the flow/kg within the normal range. The other three fetuses had decreased cardiac output with the calculated flow/kg below normal. The 15 fetuses in this group could be categorized into three types. Four fetuses had normal umbilical Doppler studies, had no perinatal complications except a low birthweight, and were thought to be genetically small infants with no evidence of placental insufficiency. The other 12 were thought to be genuinely growth retarded, but eight showed a mild elevation of umbilical artery flow ratio detected only late in pregnancy. In two fetuses there was absent diastolic flow in the umbilical artery and they also had a low cardiac output. In the remaining fetus, no umbilical artery tracing was recorded. The results in this group are summarized in Table 2.

Asymmetrical growth retardation. This was diagnosed in 16 fetuses; all of them showed greater volume of flow through the left heart than through the right heart. The mean ratio of right heart flow/combined cardiac output was 47% (SD 2·7) which was statistically significantly less than in normal fetuses ($P<0{\cdot}001$). One fetus with a normal distribution of flow showed only a slight elevation of the systolic/diastolic ratio in the umbilical artery. In all 16 fetuses the aortic mean and maximum velocity was greater than that in the pulmonary artery ($P<0{\cdot}00001$) and the values were similar to those recorded in normal fetuses ($P=0{\cdot}5$ and 0·6 respectively). The pulmonary artery maximum and mean velocities were significantly less than in normal fetuses ($P<0{\cdot}001$ and 0·01 respectively). These results are seen in Table 1. Cardiac output for gestational age was reduced or at the lower range of normal in all fetuses. This was partly due to the reduction in the mean velocity in the pulmonary artery and partly to the smaller vessel size in these small-for-dates fetuses. The measurement is squared in the calculation of volume flow, but the ratio of aorta/pulmonary artery size was not statistically significantly different from that in normal fetuses ($P=0{\cdot}2$). When corrected for fetal weight rather than gestational age, only three fetuses had low cardiac output/kg (nos 3, 9 and 13 in Table 3); all three resulted in perinatal death. There was an associated abnormal umbilical artery flow waveform in all 16 fetuses, including nine with absent or reversed flow (Table 3).

Reproducibility

The standard deviation (SD) of the difference in intra-observer reproducibility was 0·3 mm for

Table 2. Haemodynamic measurements in 15 fetuses with symmetrical growth retardation

Fetus no.	Gestation (weeks)	CCO (ml/min)	PA/CCO (%)	PA Vmax Vmean	Ao Vmax Vmean	Umb.A A/B	H/A ratio	Outcome Delivery	Outcome Gestation (weeks)	Outcome BW centile
1	35	719	56·8	70·4 19·9	74·1 17·6	4·9(↑)	1·06	CS	36	<5
2	38	995	67·3	84·0 22·0	60·0 14·8	2·6	1·05	CS	39	<3
3	37	979	68·0	60·0 17·7	65·0 14·0	2·9	1·02	CS	37	<3
4	38	939	51·3	62·0 15·0	85·0 20·2	3·4(↑)	1·03	Cs*	38	<1
5	35	815	57·0	80·0 19·6	98·0 20·7	3·9(↑)	1·07	Cs*	36	<5
6	34	608	59·0	65·0 14·9	70·0 13·6	3·7(↑)	1·08	CS*	34	<10 (pH7·2)
7	24	173(↓)	61·0	50·0 17·3	60·0 15·8	absEDF	1·15	TOP (mult. cong. abn.)		
8	20	117(↓)	50·0	60·0 14·3	70·0 19·5	absEDF	1·20	TOP		
9	39	904	60·5	60·0 17·5	70·0 15·6	3·3(↑)	1.05	SVD	39	<10
10	36	1000	55·0	80·0 23·8	98·0 20·0	3·3(↑)	1·02	CS	37	<10
11	29	300(↓)	59·0	80·0 21·1	65·0 21·1	—	1·10	CS*	29	<3
12	37	726	56·0	70·0 15·8	70·0 15·5	3·2(↑)	1·06	CS*	38	<3
13	36	875	58·0	70·0 19·9	65·0 17·8	3·2(↑)	1·00	CS*	37	<10
14	38	878	52·8	70·0 17·7	74·0 18·1	2·6	1·01	CS	39	<5
15	37	813	61·0	68·6 18·7	65·3 18·0	2·9	1·05	SVD	38	<10
Mean (SD)			58·2 (0·5)	68·7 (9·5) 18·3 (2·7)	72·6 (12·0) 17·5 (0·5)					

Abbreviations: Haemodynamic measurements (the arrows indicate values outside the normal range)· CCO, Combined cardiac output; Ao, aorta; PA, pulmonary artery; Vmax or Vmean, maximum or mean velocity; Umb.A, umbilical artery; A/B, systolic/diastolic flow ratio; absEDF or revEDF, absent or reversed end-diastolic flow.

Outcome: BW, Birthweight; CS, caesarean section; CS*, emergency CS; IOL, induction of labour; IUD, intrauterine death; SVD, spontaneous vaginal delivery; TOP, termination of pregnancy.

H/A ratio, Fetal head to abdominal circumference ratio.

Table 3. Haemodynamic measurements in 16 fetuses with asymmetric growth retardation

								Outcome		
Fetus no.	Gestation (weeks)	CCO (ml/min)	PA/CCO (%)	PA Vmax Vmean	Ao Vmax Vmean	Umb.A A/B	H/A ratio	Delivery	Gestation (weeks)	BW centile
1	35	492↓	47·4	52·0 12·0	65·0 17·3	revEDF	1·28↑	CS	35	<1
2	37	838	48·0	55·0 15·2	90·0 22·6	absEDF	1·10↑	CS	37	<1
3	29	122↓	48·3	30·0 6·2	50·0 10·7	absEDF	1·25↑	CS* (NND)	29	<3
4	24	222↓	47·2	50·0 8.90	70·0 15·1	revEDF	1·22↑	TOP	24	<5
5	35	690	47·2	60·0 13·0	70·0 14·6	6·4↑	1·16↑	IOL	36	<5
6	35	823	47·0	80·0 20·6	86·0 23·9	6·4↑	1·15↑	IOL	36	<5
7	29	374↓	48·9	54·0 15·8	70·0 19·2	revEDF	1·24↑	CS*	29	<5
8	37	885	43·1	50·0 15·9	90·0 24·1	5·4↑	1·20↑	IOL	37	<5
9	31	650↓	43·2	45·0 14·3	70·0 22·1	revEDF	1·27↑	IUD	31	<3
10	36	571	46·2	70·0 17·0	100·0 25·7	5·3↑	1·18↑	CS	36	<3
11	36	874	55·0	70·0 16·0	80·0 17·0	3·3	1·10	CS	36	<3
12	37	740	48·6	55·0 15·6	60·0 16·3	absEDF	1·20↑	CS*	38	<1
13	28	163↓	47·0	40·0 8·10	50·0 11·0	absEDF	1·25↑	IOL (NND)	29	<1
14	37	957	47·9	70·0 16·2	78·0 24·1	3·3↑	1·20↑	CS*	37	<5
15	38	816	48·0	60·0 13·7	90·0 20·9	3·4↑	1·04	IOL	38	<1
16	28	258↓	44·7	48·5 13·1	84·0 20·1	revEDF	1·38↑	CS*	29	<1
Mean (SD)			47·4 (2·7)	55·6 (12·6) 13·8 (3·6)	75·1 (14·6) 19·0 (4·6)					

For abbreviations see Table 2

both great arteries. The maximum difference of diameter measurement in the same fetus was 0·5 mm except on two occasions of the 40 paired measurements when the differences were 0·9 and 1 mm. The SD of the difference between observers for diameter measurement was 0·3 mm. For the paired 40 readings, the difference between observers exceeded 1 mm on only one occasion.

The coefficient of variation CV '(SD/mean)%' of the three measurements in each of the 10 subjects was between 0·4% and 7·6% and the mean CV in the whole group was 3·6% (expressed as the root mean square of the variabilities for each of the 10 subjects).

Discussion

The reproducibility for both diameter and velocity measurements indicates that quantitation of blood flow across the ascending aorta and pulmonary artery by cross-sectional Doppler echocardiography can be sufficiently accurate for comparison of results. The contribution to variability of calculated flow, however, is not equal for all variables influencing blood volume measurement. Important in this respect is the impact of diameter variability, which is squared in the flow formula and thus amplified. The percentage error in the blood flow estimation caused by an error in vessel diameter measurement increases with decreasing vessel size. In the human fetus in the last trimester of pregnancy, the diameter of the pulmonary artery and aorta ranges from 6 to 8 mm. An error of vessel diameter exceeding 0·5 mm should be avoided to keep the methodological error within 10–15%.

For the blood velocity measurement the reproducibility test indicates that pulsed Doppler ultrasound is a repeatable method. The size of the variation indicates that changes of blood flow velocity of 5–10% can be detected. The variability of flow due to reproducibility errors should be limited to 10–15%.

Our results support the concept of 'the brain-sparing effect' in the fetus, occurring in response to hypoxia. Reuss *et al.* (1982) and Block *et al.* (1984) found a redistribution of fetal blood flow in the fetal lamb exposed to hypoxia. In their experiments the uteroplacental bed was embolized to produce chronic hypoxia. The increased left heart flow which resulted was dependent on the degree of hypoxia and was mediated by alpha adrenergic activity. Another explanation for this redistribution of the circulation is due to changes in blood gases, when Po_2 falls and Pco_2 rises, aortic and carotid chemoreceptors are 'switched on', there is a vasodilatory response in the cerebral circulation and a compensatory vasoconstriction in the systemic circulation, especially the mesenteric and renal vascular beds (Dawes *et al.* 1968).

Our studies suggest that in the human fetus increasing placental resistance, reflected by an abnormal umbilical artery flow ratio, as well as the increase in the systemic resistance as a result of hypoxia (Jouppila & Kirkinen 1984*a*), will mainly affect pulmonary blood flow ejecting through the ductus arteriosus into the descending aorta, resulting in a fall in pulmonary artery flow velocity. This is consistent with experimental work in the fetal lamb where a decrease in right ventricular output was found by increasing the afterload either by inflating a balloon in the descending aorta (Rudolph & Heyman 1973), or by peripheral vasoconstriction by infusing methoxamine (Gilbert 1982) or phenylephrine (Thornburg & Morton 1983). In our results the aortic blood flow velocity increased as a result of vasodilatation in the cerebral and coronary circulations. Such changes in afterload produce the change in cardiac flow pattern observed in the asymmetrically growth-retarded fetus. Doppler flow studies in the common and internal carotid arteries (Marsal *et al.* 1984; Wladimiroff *et al.* 1986) in the intact human fetus demonstrate an increase in cerebral flow in asymmetrical growth retardation.

It is interesting that symmetrically growth-retarded fetuses do not redistribute their blood flow patterns Four of the 15 fetuses were thought to be genetically small fetuses without uteroplacental insufficiency; in a further eight there was only mild evidence of increased placental resistance detected in late pregnancy and it is possible that the hypoxic stimulus was not sufficiently severe or prolonged enough to result in flow redistribution. However, three fetuses showed evidence of severe growth retardation and hypoxia. Such symmetrically growth-retarded fetuses can be chromosomally abnormal, have other congenital anomalies or can be associated with intrauterine infection. It is possible that these fetuses are unable to redistribute flow either genetically or perhaps as a result of the hypoxic stimulus occurring very early in gestation.

Our findings are in agreement with those of

Rizzo *et al.* (1988), who looked at the atrioventricular valves for a change in flow pattern in growth retardation. He found that in the growth-retarded fetus the transmitral velocity was greater than the transtricuspid, a reverse of the normal. However, in a small series of growth-retarded fetuses, Reed *et al.* (1987) found an increase in pulmonary artery output and an increase in the ratio of right-sided to left-sided volume flow in the heart compared with values in the normal fetus. This contradicts other results and defies explanation. In our study the velocity of blood flow, particularly in the aorta, was well maintained until late in the course of fetal compromise. This observation is in accord with the fact that in the animal model, the myocardial and cerebral blood flow are not affected early in the course of moderate to severe hypoxia (Cohen *et al.* 1980; Peeters *et al.* 1979; Block *et al.* 1984).

In summary, evidence of a change in the pattern of flow distribution in the asymmetrical growth-retarded fetus can be demonstrated by Doppler examination of the flow velocities in the cardiac arterial valves. This redistribution appears to be a response to chronic hypoxia and allows preferential flow to the brain.

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Fetal diaphragmatic hernia: the value of fetal echocardiography in the prediction of postnatal outcome

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Summary. Nineteen pregnancies complicated by fetal congenital diaphragmatic hernia (CDH) referred for fetal echocardiography have been reviewed. Congenital heart disease was diagnosed prenatally in three fetuses; in one of these the pregnancy was terminated, the two other infants died in the neonatal period. The presence of the fetal stomach within the thorax or a hernia/heart area ratio greater than 1·7 was associated with a large diaphragmatic defect. Polyhydramnios was not associated with a poor postnatal outcome. Evidence of cardiac ventricular disproportion before 24 weeks gestation in isolated CDH was associated with 100% mortality. Development of ventricular disproportion during the third trimester was associated with a survival rate of 75%. In three fetuses, all of whom survived, no ventricular disproportion was detected during the third trimester examination.

The frequency of congenital diaphragmatic hernia (CDH) at birth is approximately 1 in 5000 (Harrison *et al.* 1978). Survival figures vary considerably. A review of recent publications suggests that if a congenital diaphragmatic hernia is diagnosed prenatally the expected survival rate varies from 10·5% (Benacerraf & Adzick 1987) to 20% (Adzick *et al.* 1985). In contrast, paediatric surgeons have reported postoperative survival rates of 82% (Hansen *et al.* 1984). The management of a pregnancy after the prenatal diagnosis of any fetal congenital anomaly can be appropriately planned if the prognosis for the anomaly is known. The usual cause of death in isolated congenital diaphragmatic hernia is pulmonary hypoplasia, but antenatal assessment of fetal lung volume is technically difficult. Prenatal detection of left ventricular hypoplasia in a fetus with congenital diaphragmatic hernia (Crawford *et al.* 1986) has prompted us to assess potential prognostic factors for fetal congenital diaphragmatic hernia.

Patients and methods

During a 3-year period, from November 1984 to November 1987, 19 pregnant women with a fetus with congenital diaphragmatic hernia were investigated by fetal echocardiography. In 14 the congenital diaphragmatic hernia had been detected during a routine obstetric ultrasound examination and this had prompted referral because of the increased risk of cardiac anomalies. In three fetuses congenital heart disease was suspected because of the abnormal ultrasound

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appearance of the fetal cardiac anatomy in the four-chamber view (Allan *et al.* 1986). Polyhydramnios was the reason for one and the diagnosis of fetal exomphalos in another referral. In each fetus the diagnosis of congenital diaphragmatic hernia was confirmed postnatally or at post-mortem.

The examination was performed using a Hewlett Packard 77020 AC phased array ultrasound system with the 5-MHz or 3·5-MHz transducer probe or an Ultramark 4 (Advanced Technology Laboratories, Inc.) with 5-MHz or 3·5-MHz sector transducer probe. Diagnosis of congenital diaphragmatic hernia was made antenatally in each case by the observation of displacement of the fetal heart and presence of an intrathoracic mass having the appearance of liver or stomach. The fetal cardiac anatomy was examined for the presence of associated congenital heart disease (Allan *et al.* 1984).

The videotape recordings of each ultrasound examination were recently reviewed systematically. Polyhydramnios as assessed by ultrasound was noted. The location of the fetal stomach and heart was recorded. In the four-chamber view plane in the fetal thorax the area of the diaphragmatic hernia and fetal heart have been planimetered as illustrated in Fig. 1. The relative size of the diaphragmatic hernia is represented by the ratio of hernia area to heart area. The fetal cardiac anatomy was also assessed for ventricular disproportion using the four-chamber view. Five still frames in end-diastole were selected for measurement of the right ventricular internal dimension (RVID) and left ventricular internal dimension (LVID) as shown in Fig. 2. The ratio of RVID to LVID was calculated for each frame and then averaged to obtain the cardiac ventricular (CV) ratio.

Details of the perinatal management and postnatal outcome have been obtained for each pregnancy. The presence of karyotypic or associated anomalies was noted from the antenatal and postnatal records.

Results

The ultrasound findings and clinical details of each pregnancy referred for fetal echocardiography are summarized in Table 1. In three congenital heart disease was diagnosed. The antenatal diagnosis of multiple anomalies (patient 1) including exomphalos, congenital heart disease (mitral atresia, ventricular septal defect and double outlet right ventricle) and left diaphragmatic hernia resulted in termination of the pregnancy. Edward's syndrome, trisomy 18, was confirmed postnatally. An atrioventricular septal defect (patient 2) and a ventricular septal defect (patient 3) were also diagnosed in association with CDH. Both infants died in the neonatal period despite intensive postnatal management.

Congenital diaphragmatic hernia was an isolated anomaly in 16 fetuses. The diaphragmatic defect was on the left in 14 and on the right in two. All the fetuses had normal cardiac connections and patent atrioventricular and arterial valves. The overall mortality in this group was 44%.

Polyhydramnios was found in six pregnancies and two of them had associated fetal structural cardiac anomalies. In the four infants with an isolated CDH, neonatal surgery was successful

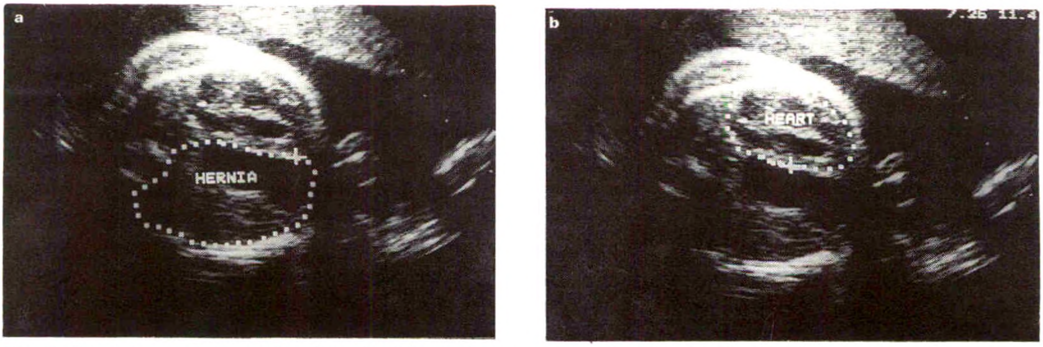

Fig. 1. Fetal thorax in 'four-chamber view' is used for assessment of the relative hernia area (hernia area/heart area). The herniated organs (a) and fetal heart (b) are planimetered using the measurement facilities on the ultrasound equipment.

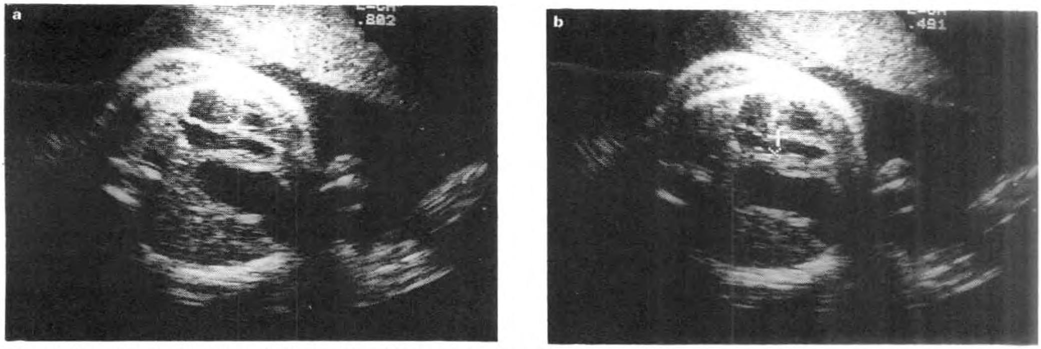

Fig. 2. Fetal heart in 'four-chamber view' is used for the assessment of ventricular disproportion (right ventricle internal dimension/left ventricle internal dimension). The internal dimension of the right ventricle (a) and left ventricle (b) are measured using the caliper facility on the ultrasound equipment.

and all are currently alive and well. A pleural effusion was drained in one fetus (no. 16).

The presence of the stomach in the thoracic cavity was noted in 14 fetuses with isolated CDH, of whom six died in the neonatal period. In two further fetuses the stomach was demonstrated in the fetal abdomen; both children are alive.

The relative hernia area was small (1·32) in one fetus. This infant did not require ventilator support before or after surgery and was discharged from hospital at 6 days. In 15 fetuses with isolated CDH the relative hernia area was greater than 1·7 and all required ventilator support. Six of these 15 infants died and the survivors needed to stay in hospital in excess of 3 weeks.

The position of the fetal heart was always altered by the presence of the herniated organs. An isolated left diaphragmatic hernia was diagnosed in 14 fetuses, and in 13 the heart was completely displaced into the right thorax. In one fetus (no. 19) a small anterior hernia, containing only liver, displaced the heart posteriorly. An isolated right diaphragmatic hernia was diagnosed in two fetuses. In fetus no. 12 the right-sided hernia deviated the heart to the left. The heart was displaced posteriorly in the thorax in fetus no. 17 so the right ventricle was adjacent to the hernia.

The CV ratio has only been assessed for those fetuses with isolated CDH, as congenital heart disease may in itself result in ventricular disproportion. The CV ratio with respect to gestational age and postnatal outcome is represented graphically in Fig.3. Seven pregnancies were examined before 24 weeks gestation. In four of these, marked ventricular disproportion was noted and all four infants died postnatally. Three newborn infants (nos 4, 5 & 6) could not be adequately stabilized on ventilator support to enable surgical correction of the defect. The fourth infant (no. 7) required ventilator support until death at 9 months. In three fetuses the CV ratio was within normal limits. One infant (no. 8) died at 2 days from bilateral respiratory distress syndrome.

In seven pregnancies the fetal cardiac appearance was studied on more than one occasion (see Fig. 3). In patient no. 6 a normal CV ratio was obtained at 18 weeks gestation but reassessment at 23 weeks gestation demonstrated an increase in the CV ratio to 1·3, outside the normal range. In three fetuses (nos 6, 9 & 15) the degree of ventricular disproportion or CV ratio increased during the third trimester.

Only when there was an abnormal CV ratio in the third trimester examination was the postnatal hospital stay in excess of 1 month. Two such fetuses died in the neonatal period; one was associated with preterm delivery at 31 weeks (no. 11). Cardiac ventricular disproportion had been noted during the third trimester in seven of the eight infants requiring a prosthetic patch to repair the large defect in the diaphragm.

In three fetuses the ventricular appearance was within normal limits on examination during the third trimester; all three were discharged within a month of birth and remain alive and well.

Discussion

The major reason for referral in this series was detection of a diaphragmatic hernia during a routine obstetric ultrasound examination. The

Table 1. The ultrasound findings and clinical details of 19 cases of congenital diaphragmatic hernia (CDH) referred for fetal echocardiography

Patient no.	Gestational age (weeks)	Fetal heart in the right chest	Polyhydramnios	Thoracic stomach	Relative hernia area*	Cardiac ventricular ratio†	Anomalies diagnosed antenatally	Outcome (length of hospital stay)
1	27	+	0	+	2·4	—	Left CDH, exomphalos, VSD, DORV, Trisomy 18	Termination of pregnancy
2	33	+	+	+	1·9	—	Left CDH, AVSD	Neonatal death
3	33	+	0	+	1·9	—	Left CDH, small VSD	Neonatal death
Examination before 24 weeks gestation (isolated CDH)								
4	23	+	0	+	2·4	2·0	Isolated left CDH	Neonatal death
5	21	+	0	+	2·9	1·5	Isolated left CDH	Neonatal death
6	18	+	0	+	1·8	1·3	Isolated left CDH	Neonatal death
7	23	+	0	+	2·4	1·4	Isolated left CDH	Infant death
8	18	+	0	+	2·1	1·0	Isolated left CDH	Neonatal death
9	18	+	0	+	2·4	1·0	Isolated left CDH	Alive (5 weeks)
10	21	+	+	+	1·9	1·0	Isolated left CDH	Alive (3 weeks)
Examination after 24 weeks gestation (isolated CDH)								
11	30	+	0	+	2·0	1·7	Isolated left CDH	Neonatal death
12	35	0	0	+	2·0	1·4	Isolated right CDH	Neonatal death
13	37	+	0	+	2·3	2·1	Isolated left CDH	Alive (2 month)
14	39	+	0	+	1·7	2·0	Isolated left CDH	Alive (2 month)
15	26	+	0	+	2·3	1·5	Isolated left CDH	Alive (2 month)
16	35	+	+	+	2·5	1·8	Isolated left CDH	Alive (1 month)
17	32	0	+	0	1·8	0·8	Isolated right CDH	Alive (1 month)
18	35	+	0	+	2·1	1·0	Isolated left CDH	Alive (3 weeks)
19	26	0	+	0	1·3	1·0	Isolated left CDH	Alive (6 days)

*Relative hernia area=hernia area/heart area.

†Cardiac ventricular ratio=right ventricular internal dimension/left ventricular internal dimension (in end-diastole).

VSD, Ventricular septal defect; DORV, double outlet right ventricle; AVSD, atrioventricular septal defect.

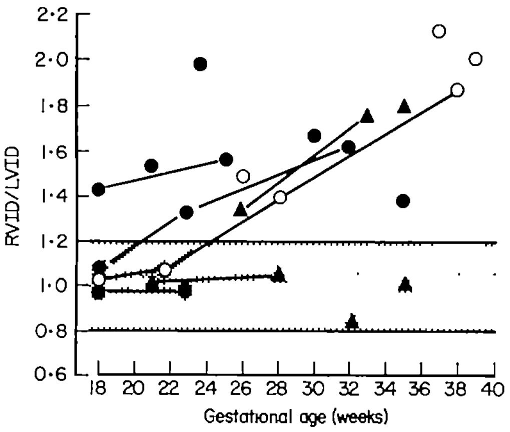

Fig. 3. Isolated congenital diaphragmatic hernia: the degree of ventricular disproportion is plotted against gestational age with respect to postnatal outcome. Ventricular disproportion is defined as right ventricular internal dimension/left ventricular internal dimension (RVID/LVID); the shaded area indicates the normal range of values. ●, Postnatal death; ○, alive (over 1 month in hospital); ▲, alive (short hospital stay).

routine use of the four-chamber view of the fetal heart is encouraged (Allan *et al.* 1986) for the early detection of severe congenital heart disease. Abnormal orientation of the fetal heart or the presence of additional cystic structures within the fetal chest can result in the prenatal diagnosis of congenital diaphragmatic hernia in the second trimester. Parents and the obstetrician need information indicating the prognosis of an individual lesion, particularly if termination of the pregnancy is being considered.

Our results suggest that polyhydramnios in association with isolated defects does not indicate a poor prognosis. In this series polyhydramnios was noted in a total of six pregnancies (33%). In those where the congenital diaphragmatic hernia was an isolated anomaly all children are alive and well. This finding is in marked contrast to the series described by Adzick *et al.* (1985) where polyhydramnios was the referral reason in 66% and was suggested as a predictor for a poor clinical outcome.

In the present series, antenatal diagnosis of congenital heart disease was made in three pregnancies (16%) and was related to a poor postnatal outcome. Benacerraf & Adzick (1987) diagnosed associated karyotypic or multiple anomalies prenatally in nine fetuses (47%). The presence of chromosomal or additional anomalies, including congenital heart disease, indicates a poor outcome, and termination of the pregnancy may be an appropriate option.

The site of the fetal stomach has prognostic importance, and an abdominal site indicates a good prognosis. In isolated congenital diaphragmatic hernia a survival rate of 100% was associated with an abdominal site. A survival rate of 50% was associated with a thoracic site and most (75%) of these infants required a prosthetic patch to close the defect in the diaphragm.

The size of an isolated congenital diaphragmatic hernia is of value in predicting outcome, and the smaller lesions were associated with the most optimistic prognosis. Antenatal diagnosis of a small anterior Morgagni hernia is seldom associated with postnatal respiratory problems. This type of lesion has an excellent prognosis.

The detection of cardiac ventricular disproportion in isolated CDH indicates a poor prognosis. Ventricular disproportion first noted during the second trimester was associated with a very poor outcome (100% mortality) and suggests the presence of irreversible pulmonary hypoplasia. Development of ventricular disproportion during the third trimester was associated with a large defect in the diaphragm requiring repair using a prosthetic patch, a more lengthy hospital stay and a 25% mortality. The absence of ventricular disproportion in the third trimester suggests a good prognosis. The onset and degree of ventricular disproportion appear to be related to the degree of pulmonary hypoplasia. This could prove to be the most useful prognostic indicator in cases of isolated congenital diaphragmatic hernia.

Ventricular disproportion first noted in the third trimester indicates moderately severe pulmonary hypoplasia, and specialized intensive care facilities will be required at the time of delivery. Antenatal transfer of these patients would enable optimum postnatal care but the prognosis must be guarded and a prolonged stay in hospital should be anticipated. Unforeseen postnatal pulmonary complications, such as respiratory distress syndrome, will further compromise pulmonary function and may result in a poor outcome.

The aetiology of the cardiac ventricular disproportion is still unresolved. Ventricular hypoplasia in association with congenital diaphragmatic hernia was first described at autopsy by Siebart *et al.* (1984). These authors suggested that herniated organs were causing compression of the left ventricle as the defect affected the left diaphragm in each case. Ventricular hypoplasia could also be caused by altered haemodynamics secondary to the hernia. Distortion of the thoracic veins (Crawford *et al.* 1986) may result in a reduction in the volume of blood shunted through the foraman ovale, the antenatal intra-atrial communication. Alternatively, compression of the developing fetal lung may inhibit the concomitant development of peripheral branches of the pulmonary arteries. A reduction in the volume flow in the pulmonary veins may similarly cause reduced flow through the left atrium and ventricle (Allan *et al.* 1988). The investigation of blood flow using Doppler techniques and the observation of the ventricular disproportion where right- and left-sided defects are present may help to clarify the aetiology of this reversible form of ventricular hypoplasia.

Antenatal diagnosis of congenital diaphragmatic hernia by routine obstetric ultrasound can alter the obstetric management of the pregnancy. The presence of chromosomal or additional cardiac anomalies was associated with a poor outcome, and termination of the pregnancy should be considered. Karyotyping by amniocentesis or fetal blood sampling and ultrasound examination for fetal anomalies, including referral for fetal echocardiography, is recommended. In isolated diaphragmatic hernia, pulmonary hypoplasia is the usual cause of death in the infant. The degree of pulmonary hypoplasia may be predicted by observing both the gestational age at onset of ventricular disproportion and its severity. When the diaphragmatic hernia is isolated, fetal echocardiography should be repeated at 23 and 32 weeks gestation to assess the prognosis more accurately. Our results suggest that in selected cases of fetal diaphragmatic hernia the prognosis can be good and fetal echocardiography has an important role to play in the prediction of postnatal outcome.

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Plasma beta-endorphin concentrations during suckling in lactating women

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Summary. Beta-endorphin appears to be involved in the hormonal response to suckling in some animals. The peripheral secretory patterns of β-endorphin, prolactin and cortisol were investigated in serial venous blood samples taken during suckling from eight healthy women who were breast-feeding on the third or fourth day of the puerperium. Plasma levels of prolactin and β-endorphin increased significantly during suckling reaching a peak after 20 min, levels of cortisol remained unaffected. It is suggested that the increased β-endorphin derives from an extra-hypophyseal source.

It has been reported in animals that suckling increases plasma levels of prolactin (PRL), growth hormone (GH) and cortisol (Voogt *et al.* 1969; Saunders *et al.* 1976), whereas gonadotrophin levels decrease (Isherwood & Cross 1980). This hormonal response is similar to that evoked by opiate peptides (Morley 1981) and suggests that endogenous opiate peptides are implicated in the control of the hormonal response induced by suckling. In fact, it has been demonstrated that in the ewe there is a close correlation between suckling bouts and portal beta-endorphin and peripheral PRL concentrations, suggesting a hypothalamic effect of beta-endorphin itself (Gordon *et al.* 1987). Furthermore, it has been shown in animals that suckling is able to induce an increase in plasma beta-endorphin levels (Riskind *et al.* 1984). The aim of the present study was to measure the peripheral secretory patterns of beta-endorphin, PRL and cortisol in a group of nursing women, before and after suckling.

Subjects and methods

Eight healthy women (24–36 years), who had given birth to normal infants, were studied. Informed consent was previously obtained from each.

Tests were performed on the third to fourth day postpartum, in order to exclude a possible interference of stressful factors related to parturition. Venous blood samples (4–6 ml) were obtained in basal conditions and at 5, 10, 20, 30, 45, 60 and 90 min after the onset of suckling. The duration of suckling was 20–30 min. Blood samples were collected in ice-chilled glass tubes which contained aprotinin (250 k-units) and EDTA (7 mg). The blood was centrifuged at 4°C, and the plasma obtained was frozen and stored at −40°C.

Plasma immunoreactive beta-endorphin concentrations were measured by RIA. Plasma

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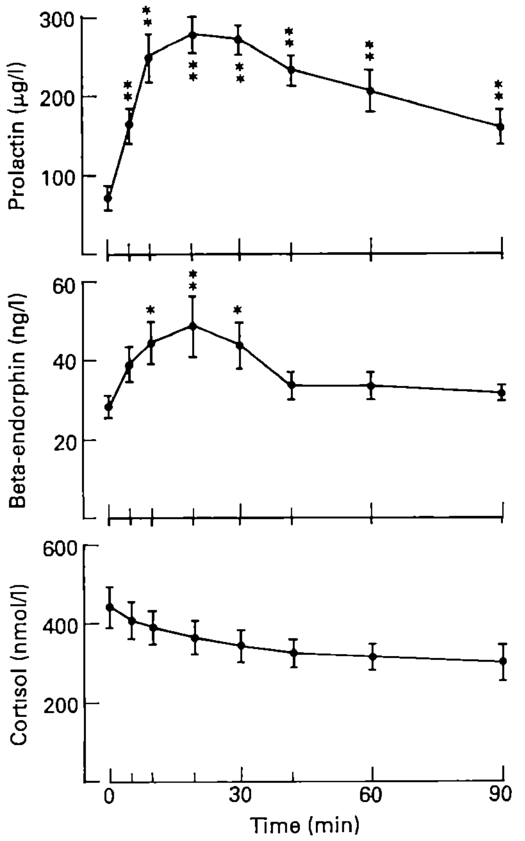

Fig. 1. Plasma prolactin, beta-endorphin and cortisol values in basal conditions and after the start of suckling in eight women. $*P<0·05$ and $**P<0·01$ *vs* basal values.

beta-endorphin was first extracted and concentrated by immunoaffinity chromatography. The smallest detectable concentration was 8·5 ng/l; the intra- and inter-assay coefficients of variation were 6·5 and 18·1%, respectively. In our laboratory, plasma beta-endorphin values were 29·4 (SEM 1·8) ng/l and 28·4 (SEM 1·4) ng/l in adult females and in non-lactating women, respectively.

Plasma PRL and cortisol levels were also measured by a RIA method; the intra- and inter-assay coefficients of variation were less than 10% and the assay sensitivities were 1·5 µg/l and 27·6 nmol/l for PRL and cortisol, respectively.

Statistical analysis was performed using the one-way analysis of variance, followed by the two-tailed Student's *t*-test for unpaired observations.

Results

Data obtained are illustrated in Fig. 1. Plasma PRL concentrations showed a sharp increase ($F = 15·536$; $P<0·01$) noted 5 min after the start of suckling, and reaching the highest levels at 20 min (mean 281·9, SEM 21·7 µg/l; $P<0·01$). Mean plasma beta-endorphin values in basal conditions were 27·3 (SEM 1·6) ng/l, and were significantly increased ($F = 3·168$; $P<0·01$) after suckling to reach a peak value at 20 min (mean 48·2, SEM 6·6 ng/l; $P<0·01$).

Plasma cortisol levels were unaffected by suckling.

Discussion

Data obtained demonstrate that in humans suckling is a stimulus able to induce beta-endorphin release. The possibility that this release may be influenced also by psychological factors or by mother–infant contact cannot be excluded at present. However, the timing of the beta-endorphin increase does not seem to support this possibility. Furthermore, these results are in agreement with previous experimental studies which showed a rise in plasma beta-endorphin induced by suckling in the rat (Riskind *et al.* 1984).

In our study the increase of plasma beta-endorphin levels occurred independently from plasma cortisol variations. It is known that ACTH, beta-endorphin and the other related peptides are derived mainly from the common pituitary precursor pro-opiomelanocortin, and are secreted concomitantly by the pituitary gland (Gillies *et al.* 1980). Furthermore, it is known that in man plasma beta-endorphin fluctuates concomitantly with plasma ACTH and cortisol during the day (Rolandi *et al.* 1987*a*). Thus, the hypothesis that the beta-endorphin secreted during suckling is derived from extra-hypophyseal sites can be proposed. In fact, previous studies have demonstrated that circulating beta-endorphin is derived, in part, from peripheral sources, such as the gut (Larson 1977), pancreas (Bruni *et al.* 1979) and adrenal medulla (Boader & McHardle 1985), and that during suckling there is an increase of some gut hormones, such as gastrin, cholecystokinin and VIP (Linden *et al.* 1987; Rolandi *et al.* 1987*b*). Based on the present study, it appears possible that beta-endorphin secretion, evoked by suckling, also reflects the hormonal gastrointestinal release. The significance and the role of this beta-endorphin secretion is at present unclear. However, since in humans beta-endorphin crosses the blood-brain barrier (Gerner *et al.* 1982) and is able to stimulate PRL release (Schulz *et al.* 1980) and to inhibit gonadotrophin secretion (Kalra & Kalra 1985), its possible role in the suckling-induced PRL rise and in mediating the lactational amenorrhoea can be suggested.

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The course and outcome of pregnancy after ovarian electrocautery in women with polycystic ovarian syndrome: the influence of body-weight

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Summary. In 89 women with polycystic ovary syndrome (PCOS) who conceived after ovarian electrocautery, the pregnancy continued beyond 31 weeks in 62. In this group the frequency of pre-eclampsia and diabetes was 12·9 and 8·1% respectively. The increased frequencies were confined to overweight women. The frequency of major and minor malformations was 1% and 3·8% respectively. The rate of early miscarriage of the first pregnancy after ovarian electrocautery was 15%, and when later pregnancies were included the rate reduced to 10·3%. These data do not indicate any impact upon the course or outcome of pregnancy from the state of PCOS *per se* or the ovarian electrocautery that induced ovulation in this series.

The treatment of the Stein–Leventhal syndrome, the polycystic ovary syndrome (PCOS) with respect to fertility has been relatively rewarding, whether surgical (wedge resection) or drug (clomiphene citrate) treatment has been used. A further improvement of the pregnancy rate was achieved by the introduction of laparoscopic ovarian electrocautery (Gjønnæss 1984).

In the original description of PCOS by Stein & Leventhal (1935), obesity was a cardinal sign. Women with PCOS also show an increased prevalence of pre-eclampsia (Diamant *et al.* 1982). Obesity *per se* and high weight gain during pregnancy have also been associated with such pregnancy complications as hypertension, pre-eclampsia and diabetes (Edwards *et al.* 1978; Hytten & Leitch 1971; MacGillivray 1983; Spellacy *et al.* 1986; Shepard *et al.* 1986). One purpose of the present study was to record the course of pregnancy in women with PCOS, with emphasis on body-weight.

Women with PCOS show increased rates of miscarriage, fetal malformation and multiple pregnancy (Ahlgren *et al.* 1976; Garcia *et al.* 1977; Diamant *et al.* 1982), but whether this is associated with the disease or the treatment has not been settled. It is not certain that those rates are necessarily increased after drug treatment (Harlap 1976; Kurachi *et al.* 1983) or wedge resection (Pietrusiewicz 1981). A second aim of this work, therefore, was to record the fetal outcome of pregnancy after ovarian electrocautery in women with PCOS.

Patients and methods

All the 190 women with PCOS treated by ovarian electrocautery (Gjønnæss 1984) in the gynaecological department, Aker Hospital, from 1976 have been followed for up to 10 years; 89 of them conceived during this period.

The diagnosis of PCOS was based on: menstrual irregularities, an endocrine profile showing progesterone values with no luteal phase, serum concentrations of luteinizing hormone (LH) >12 iu/l and androgenic hormones in the upper or increased 'physiological range' and low sex-hormone-binding globulin. In addition, the

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Table 1. Pre-eclampsia and diabetes, related to body-weight in 62 women who reached at least 31 weeks gestation in their first pregnancy after ovarian electrocautery

			Body-weight (kg)							
Obesity			8 weeks		32–40 weeks		Pre-eclampsia		Diabetes	
grade	*n*	(%)	Mean	(SD)	Mean	(SD)	*n*	(%)	*n*	(%)
0	34	(55)	58·6	(7·3)	70·3	(8·7)	2	(6)	0	(—)
1	16	(26)	72·1	(7·2)	84	(7·5)	2	(13)	2	(13)
2/3	10	(16)	84·1	(6·1)	101·9	(13·6)	4*	(40)	3*	(30)
Unknown	2	(3)								
All	62		67·7		80·7		8	(13)	5	(8)

*One woman developed both pre-eclampsia and diabetes

Of the 34 normal-weight women, 26 (76%) were nulliparous, and of the 26 obese women 18 (69%) were nulliparous.

characteristic appearance of the ovaries was observed in all patients.

Of the 89 women who became pregnant, 76 (85%) conceived within 1 year after the ovarian electrocautery, 52 (58%) within the first 6 months, and only two took >2 years to conceive. For five women who used oral contraceptives for 1–3 years after the ovarian electrocautery the time interval from the cessation of drug treatment was recorded. All the women were followed closely during pregnancy. Most were examined and interviewed by the author in connection with the delivery or during the first postpartum week, and nearly all of them at the 6-week postpartum follow-up.

Pre-eclampsia was defined as a blood pressure >140/90 mmHg on two or more occasions and proteinuria. The diagnosis of gestational diabetes was based on a pathological glucose tolerance curve. The fasting patients were given 75 g of glucose orally, and when the blood glucose level after 2 h was higher than 8·5 mmol/l, gestational diabetes was recorded. Obesity was classified according to the chart prepared by Garrow (1981) which is based on the relation between body-weight and height: grade 0 represents normal weight and grade 3 severe overweight. The women were classified at the time of ovarian electrocautery, 49 were grade 0, 24 grade 1, nine grade 2 and three grade 3. In four women body-weight was not recorded. Mean ages in the four body-weight groups were 26·9, 25·9, 27·0 and 27·7 years, respectively. The fetal data were taken from the hospital records, including neonatal screening by an experienced paediatrician. This information was supplemented by the maternal information given at the postpartum interview.

Statistical significance was tested using χ^2 with Yates' correction or Fisher's exact test, $P<0·05$ being considered statistically significant.

Results

Of the 89 women with PCOS who conceived 36 were obese. The interval between the ovarian electrocautery and the pregnancy was not influenced by body-weight. Mean body-weight was 67·7 kg, and the mean weight gain during pregnancy was 13 kg. The weight increases were related to the original body-weight of the women; the heaviest women gained the most weight. The mean age of the patients was not important in this context, and the proportions of women >30 years of age in weight groups 0, 1 and 2/3 were 31% (15/49), 12% (3/24) and 25% (3/12), respectively. The mean blood pressure of the women was normal early in pregnancy (125/76 mmHg), none of the women exceeding 140/90 mmHg. In late pregnancy the mean blood pressure of the whole group was unchanged (125/80), even though some women with pre-eclampsia had a blood pressure up to 160/110 mmHg.

The development of pre-eclampsia was not related to the original blood pressure but there was a significant relation with body-weight (Table 1) ($2P = 0·0397$, Fisher) when the women in weight group 2/3 were compared with those of normal weight. Of the obese women grade 3, one developed pre-eclampsia and two developed gestational diabetes. The mean age of the pre-eclamptic women was 26·8 years, the oldest was 30 years of age.

Diabetes was not seen in any of the women with PCOS before the ovarian electrocautery,

Table 2. Outcome of the first pregnancy after ovarian electrocautery

				Gestation (weeks)					
				<16			16–31		32–41
Obesity grade	*n*	Maternal age (years) Mean	(SD)	Miscarriage	Therapeutic abortion	Tubal pregnancy	Stillborn	Alive	
0	49	26·8	(4·9)	6	1	4	2	2*	34
1	24	26·8	(4·3)	5	1	1	1		16
2/3	12	27·6	(3·2)	1			1		10
Unknown	4			1			1		2
Total	89			13	2	5	5	2*	62

*One infant died of respiratory distress syndrome and one survived and developed normally.

but appeared during the pregnancy significantly more often in those who were overweight than in those with normal weight ($2P = 0{\cdot}0206$, Fisher) (Table 1). Their mean age was 27·0 years and only one woman was more than 30 years of age.

In the first pregnancy that continued beyond 16 weeks gestation after the ovarian electrocautery, the perinatal mortality, including all stillbirths and first week neonatal deaths, was 8·7% (6/69). Of the six perinatal deaths four occurred at 20 or 21 weeks gestation, one at 28 weeks and one at 34 weeks associated with placental abruption. Obesity itself did not influence perinatal mortality. The percentage of women in weight groups 0, 1 and 2/3 who had living infants was 71% (35/49), 67% (16/24) and 83% (10/12) respectively (Table 2).

Of the 62 women whose pregnancies continued beyond 31 weeks 17 (27%) were >30 years of age (mean age 27 years); 13 (21%) were delivered by caesarean section, which is a higher rate than that reported in the general Norwegian population (10·6% in 1985, $P = 0{\cdot}039$) and in our department (mean for the last 10 years: 12%, $P = 0{\cdot}09$). The indications for caesarean section were imminent asphyxia in three pregnancies, breech presentation and/or pelvic disproportion in four, dystocia in four, diabetes with pre-eclampsia in one woman and placenta praevia in one. The mean age of this group was 26·8 years.

The 13 pregnancies that ended in early miscarriage before 16 weeks gestation showed no special features (Table 2). Two of them were recorded as 'hormonal pregnancies' only, and one had a hydatidiform mole. Thus, the early miscarriage rate of the first pregnancy after ovarian electrocautery in women with PCOS was 15% (13/89). The mean age of these 13 women was 28·9 years; four were >30 years of age. Four of the five patients with tubal pregnancy (mean age 28 years) had tubal surgery. Of the seven women with late miscarriages or threatened miscarriage (Table 2) (mean age 26 years), three had placental abruption, one of whom gave birth to a living infant who died from respiratory distress syndrome after 20 h. None of these women had pre-eclampsia. Three women had cervical incompetence, and subsequently two have accomplished a full-term pregnancy with a Shirodkar cerclage. The seventh woman had premature rupture of the membranes at 22 weeks gestation. She was treated with antibiotics and tocolytics, and gave birth to a healthy girl, birthweight 1300 g at 30 weeks gestation (this child showed normal development at 2·5 years of age). Two women developed polyhydramnios, one in connection with pregnancy diabetes, but the pregnancies and the infants were otherwise normal.

Of the 89 women with PCOS, 29 conceived at least once subsequently (Table 3). Without knowledge of the observation time or contraception, this percentage cannot be regarded as an index of fertility subsequent to the first pregnancy after ovarian electrocautery. No attempt was made to record 'hormonal pregnancies'. In all 29 women the pregnancy continued beyond 34 weeks, and only one baby was lost. Of the nine women who had pre-eclampsia during their first pregnancy, only three have become pregnant again and none of them developed pre-eclampsia.

Thus, the cumulated early miscarriage rate in 89 women with PCOS who conceived once or several times after ovarian electrocautery was 10·3% (13/87+0/39 = 13/126), correction being made for two therapeutic abortions. The uncor-

Table 3. Infants born after ovarian electrocautery in 89 women with polycystic ovary syndrome*

Pregnancy after electrocautery	Number of infants			
	Male	Female	Sex unknown	Total
First	35†	28	1	64
Second	14‡	10	5	29
Third	3§	6	1	10
Fourth		1		1
	52	45	7	104†‡§

*The table does not include five stillbirths before 28 weeks gestation.

†One infant died of respiratory distress syndrome 20 h after vaginal delivery induced by placental abruption following a maternal trauma at 28 weeks.

‡One infant died *in utero* after placental abruption at 34 weeks, birthweight 2290 g, and otherwise normal. Obesity grade 1.

§One infant died *in utero* after placental abruption in pregnancy week 39. Obesity grade 1.

rected perinatal mortality, including all pregnancies continuing beyond 16 weeks gestation, was 7·3% (8/109) (Tables 2 and 3). Of the 129 pregnancies, 104 continued beyond 28 weeks gestation and three of these infants were lost (Table 3). There was a slight excess of males and no twins (Table 3). The infants showed no special features. Birthweight of term infants was related to the maternal weight, the mean birthweights in the four groups with obesity grades 0, 1, 2 and 3 were 3506, 3719, 3766 and 4123 g, respectively. In the whole series, one infant was born with serious malformations. The mother was 30 years old, gave birth to a boy (3520 g) with osteogenesis imperfecta after 40 weeks uneventful pregnancy. He had multiple malformations and died after a few months. One year later she gave birth to a normal boy, and 2 years after that to a normal girl. One woman had a boy with a minor degree of facial asymmetria. She was obesity grade 2, her weight increased from 80 to 105 kg during her pregnancy, and she developed pre-eclampsia and diabetes. One boy had a transient cardiac murmur, which was not clinically significant, and one girl had a positive Ortolani's sign of a moderate degree. The girl who was born 8 weeks after rupture of the membranes showed a malposition of the left fifth toe, probably an effect of local pressure. No other abnormality was found in the infants of this series. So, the rates of minor and major malformations were 3·8% (4/104) and 1% respectively.

Discussion

Pregnancy complications such as pre-eclampsia and diabetes were relatively frequent in this series of women with PCOS (12·9 and 8·1%, respectively), the difference from the general pregnancy population of Norway (3·8 and 0·25%) (Medical Birth Registry of Norway 1985) being statistically significant ($P = 0{\cdot}0012$ and $P < 0{\cdot}001$, respectively). These incidences could not be related to the pre-pregnancy blood pressure or the age of the patient. In this series 25% of the women were 30 years or more, and in the general pregnant population this percentage was 32%.

Overweight, however, seemed important, which is in agreement with reports on unselected, elderly, or obese pregnant women (Hytten & Leitch 1971; MacGillivray 1983; Spellacy *et al.* 1986; Shepard *et al.* 1986; Edwards *et al.* 1978). Diamant *et al.* (1982) reported an increased rate of pre-eclampsia in 33 women with PCOS who conceived after treatment with clomiphene citrate and gonadotrophins or both. However, as these investigators did not record the prevalence of obesity in their series, and obesity is frequently connected with PCOS, their observation might also be related to the body-weight of the women.

In our series the frequency of pre-eclampsia in women with PCOS and normal weight was 5·9% which is not significantly different from the rate of 4% reported by Diamant *et al.* (1982) for their control series or the rate of 5·8% reported by Edwards *et al.* (1978) for their normal-weight group or the rate of 5·4% reported for the general pregnancy population of Norway (Medical Birth Registry of Norway 1985).

In our series none of the normal-weight women with PCOS had gestational diabetes, whereas the rate is 0·25% in the general pregnancy population of Norway. The overweight women had a frequency of gestational diabetes of 19% which compares well with the rates of 10·6% in obese and 2·8% in non-obese women reported by Edwards *et al.* (1978). Even if the mean parity of the general pregnancy population was higher, these differences between normal-weight and overweight cases could probably not be related to the parity, which was similar in the two groups (Table 1). Pregnancy weight gain was also related to maternal body-weight, and similar to that found in the general Scandinavian population (Westin 1977).

So, in the course of pregnancy after ovarian electrocautery, no difference from the normal could be demonstrated that was caused by the PCOS or the treatment. Increased frequencies of pre-eclampsia and diabetes were found in overweight women, but the normal-weight women did not differ from the general population.

There is no agreement about increased frequency of congenital malformations in the offspring of women with PCOS. Ahlgren *et al.* (1976) observed an increase after clomiphene citrate treatment, and because the increase was similar to that seen after treatment with gonadotrophins they concluded it was more likely to be associated with the subfertility than with a drug effect. In contrast, and in a larger series, Kurachi *et al.* (1983) and Harlap (1976) found no significant association between rate of malformations and treatment with clomiphene or gonadotrophins or both. Following ovarian electrocautery in PCOS, no special feature characterized the infants. The frequencies of major and minor malformations (1% and 3·8%) are lower than those found in the general population of Norway (5·3% and 9·7%) (Medical Birth Registry 1985). An increase in multiple pregnancies has been reported after clomiphene treatment by Ahlgren *et al.* (1976), whereas there were none in the present series. The sex ratio of 1·16 (Table 3) is similar to that in the general population (1·06) (Medical Birth Registry 1985; James 1985), and in contrast to the decreased sex ratio (0·85) reported for pregnancies after ovulation induction with clomiphene or gonadotrophins (James 1985). The association between the pre-pregnant weight, the maternal weight gain and the birthweight was similar to that reported for the general population (Abrams & Laros 1986).

The early miscarriage rate in the first pregnancy after ovarian electrocautery was 15%. The miscarriage rates found in clomiphene-induced pregnancies varied between 11·2 and 25·3%, and after treatment with clomiphene or gonadotrophins, or both, between 19·4 and 28·5% (Ahlgren *et al.* 1976; Garcia *et al.* 1977; Kurachi *et al.* 1983; Ben-Rafael *et al.* 1983). Following wedge resection of the ovaries, a rate of 15% has been reported (Pietrusiewicz 1981). However, difficulty in assessing true miscarriage rates is well known, some of the very early miscarriages being unrecognized. Whereas the WHO Scientific Group (1970) reported 15–20 miscarriages per 100 pregnancies to be 'a reasonable estimate', more recent estimates suggest a loss of 62% conceptuses before 12 weeks gestation (Edmonds *et al.* 1982). So, the early miscarriage rate of 14·6% for the first pregnancy, and the cumulated early miscarriage rate of 10·3% for women with PCOS who conceived more than once after ovarian electrocautery, compare favourably with the general population.

In conclusion, pregnancy complications in women with PCOS, such as pre-eclampsia and diabetes, are related to body-weight and not to the state of PCOS or the treatment by ovarian electrocautery. In pregnancies following ovarian electrocautery there is no increase in the rates of miscarriage, fetal malformation or multiple pregnancy.

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Immunohistochemical determination of tumour growth fraction in human ovarian carcinoma

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Summary. The proportion of proliferating tumour cells in a tumour ('growth fraction') was estimated in 30 patients with primary ovarian carcinoma, using monoclonal antibody Ki-67 which reacts with a nuclear antigen present only in proliferating cells. A positive correlation between the 'growth fraction' and both the clinical stage and histological grade of the tumours was observed. A high 'growth fraction' was observed in advanced, metastatic and poorly differentiated tumours and a low 'growth fraction' with early stage, well-differentiated tumours. This information which has not been available previously to clinicians may be of practical value for determining the prognosis, and influencing treatment recommendation.

Most patients with ovarian cancer present with advanced stage disease, when the probability of cure is small. Chemotherapy is widely used in patients with advanced disease but complete response remains unusual even with the most toxic drug combinations. Some means of identifying patients with drug-sensitive tumours would assist in the treatment selection, and in defining patients with different prognoses.

Pathological characteristics are used to predict the behaviour of a cancer and the prognosis. Poorly differentiated tumours usually have a rapidly progressive course and early dissemination. These tumours tend to be more sensitive to radiotherapy and chemotherapy than their well-differentiated counterparts. However, the histological classification is very subjective depending on the knowledge and experience of the pathologists and the precise criteria used. Nevertheless, the Princess Margaret group in Toronto incorporate pathological type and tumour grade in their treatment decision (Dembo 1984). The proliferative activity of human tumours has been well studied and found to be an indicator of aggressiveness, and to be related to the course of disease and the response to chemotherapy (Muggia *et al.* 1974). Numerous methods have been applied to study this prognostic variable including thymidine labelling index, mitotic index, DNA flow cytometry (Iversen & Skaarland 1987), and in-vivo BrUdR labelling (Tada *et al.* 1986). The conventional radioisotope and autoradiography studies of growth fraction of human tumours have raised both practical and ethical problems. Most of these methods are also time consuming and/or require expensive equipment or reagents. Recently, Gerdes *et al.* (1984) have utilized immunocytochemical techniques and a monoclonal antibody to identify proliferating cells in G1, S, G2 and M phases of the cell cycle. Their antibody Ki-67 reacts with a nuclear antigen present in all proliferating cells but absent in quiescent cells. Their various studies have reported a highly significant cor-

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relation between the proportion of Ki-67 positive cells and the histological classification of malignant non-Hodgkin lymphomas (Gerdes *et al.* 1984), breast tumours (Gerdes *et al.* 1986) and lung tumours (Gatter *et al.* 1986). The commercial availability of Ki-67 monoclonal antibody has stimulated further reports of the use of this antibody to study various tumours (McGurrin *et al.* 1987; Schrape *et al.* 1987). However, to our knowledge, other than one recent paper (Brown *et al.* 1988), no other study on the growth fraction in gynaecological tumours has been reported. In this paper, we report an immunohistochemical study of the growth fraction of ovarian carcinomas using monoclonal antibody Ki-67 and its correlation with their histological characteristics.

Subjects and methods

Tumours from 30 women with ovarian cancer who were attending the King George V Hospital, Sydney, Australia, between August 1986 and July 1987 were studied. The histological grades by two pathologists were well differentiated (3 tumours), moderately differentiated (14 tumours) and poorly differentiated (13 tumours). The histological grading was based primarily on the architectural pattern and not on the cytological atypia of the epithelial lining cells according to the criteria described by Czernobilsky (1987).

Frozen sections of the tumour specimens were stained with the monoclonal antibody Ki-67 using the immunoperoxidase method as recommended by Hsu *et al.* (1981). Briefly, 6-μm-thick frozen sections were mounted on gelatine-coated slides, and immediately fixed in 100% acetone for 10 min. Non-specific staining was blocked with non-immune horse serum. The sections were then incubated with either the monoclonal antibody Ki-67 or a control monoclonal antibody without affinity for the nuclear antigen. Thereafter, the slides were incubated with a bridging antibody, an avidin–biotin–peroxidase complex, and finally with diaminobenzidine–hydrogen peroxide substrate for the detection of the antibody staining. The sections were finally counterstained with haematoxylin. A quantitative method was used to determine the proportion of Ki-67 positive cells in each section. The number of positive nuclear staining cells was counted in 500 tumour cells seen in the high-power field (×400 magnification). The average of three counts over the same slide was used to determine 'growth fraction' in the tumour.

In six patients there were biopsy specimens from more than one tumour site. In three patients the primary ovarian tumour and secondary omental or peritoneal tumours were available and in the other three the distant metastatic tumour in bone, liver, or skin. The growth fraction of tumours in these sites was estimated to determine any variation of the same tumour at different sites.

Statistical analysis used Student's *t*-test to determine the significance of differences in growth fraction observed between the different histological grades.

Results

Figure 1a shows the immunostaining pattern in an ovarian carcinoma with a low growth fraction as gauged by staining. Figures 1b and 1c show the immunostaining patterns with Ki-67 in tumours, with moderate and high nuclear staining. It can be seen that the staining using Ki-67 is predominantly nuclear. In general, the stained cells show a higher degree of nuclear irregularity, pleomorphism and mitotic activity compared to the non-stained cells.

Figure 2 shows the Ki-67 staining values in tumours grouped according to their histological grade. In the well-differentiated tumour, the mean of nuclear staining with Ki-67 was 6·6% (SD 3·3%). There were three tumours in this group with Ki-67 staining values of 2·8%, 7·9% and 9·0%. The mean value of moderately differentiated carcinoma was 27·2% (SD 12·9%), with a range between 9·6% and 58·3%. The poorly differentiated carcinoma had a mean Ki-67 staining value of 40·3% (SD 13·7%) with a range from 24·5% to 73·5%. The difference between these groups was significant ($P<0·05$). The Ki-67 staining values according to tumour stage are also shown in this figure. It appears that tumours with higher Ki-67 staining are most common with the advanced clinical stage IV.

Figure 3 shows similar Ki-67 staining values of primary tumours and omental or peritoneal tumours, but there are significant differences between the mean Ki-67 staining values of the primary tumour and that of the distant metastatic sites ($P<0·05$).

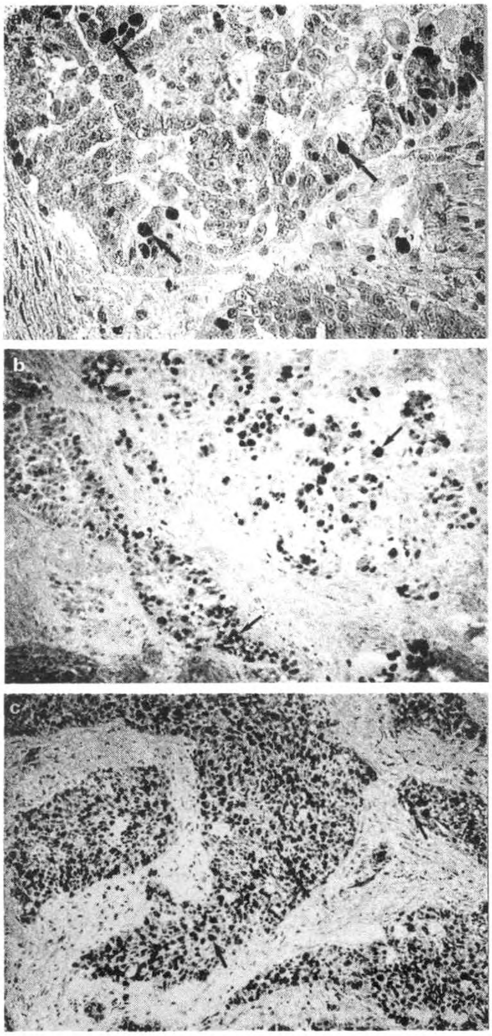

Fig. 1. Immunostaining with Ki-67 of frozen tissue sections of ovarian carcinomas. Prominent nuclear staining is present in some tumour cells (indicated by arrows). The growth fraction represents the percentage of Ki-67 positive cells in 500 tumour cells determined. (a) Well-differentiated tumour, with low growth fraction (×150). (b) Moderately differentiated tumour, with moderate growth fraction (×95). (c) Poorly differentiated tumour, with high growth fraction (×95).

Discussion

Mendelsohn (1962) defined the growth fraction (*GF*) as the relation between the number of proliferating cells (*P*) and the total number of cells including quiescent (*Q*) cells which are out of the mitotic cycle where

$$GF = P/P+Q$$

The growth fraction of various human cancers was estimated with a monoclonal antibody Ki-67 by Gatter *et al.* (1986) and Gerdes *et al.* (1983, 1984). They demonstrated that this antibody bound to all proliferating cells, such as lymphocytes, macrophages, renal cells, sperm cells, but not to quiescent cells. In flow cytometric studies, they showed a steady increase of Ki-67 labelled cells in peripheral blood lymphocytes when they were stimulated to proliferate by phytohaemagglutinin. Moreover, Ki-67 labelling disappeared from HL 60 cells when they were stimulated to differentiate into mature macrophages (Gerdes *et al.* 1983). Schwarting *et al.* (1980) also reported a simultaneous increase in Ki-67 labelling and [3H]-thymidine uptake by blast cells stimulated by concanavalin (correlation coefficient of 0·98). Together these findings indicate that Ki-67 stains proliferating cells.

We observed a significant correlation between the histological grading and the mean value of

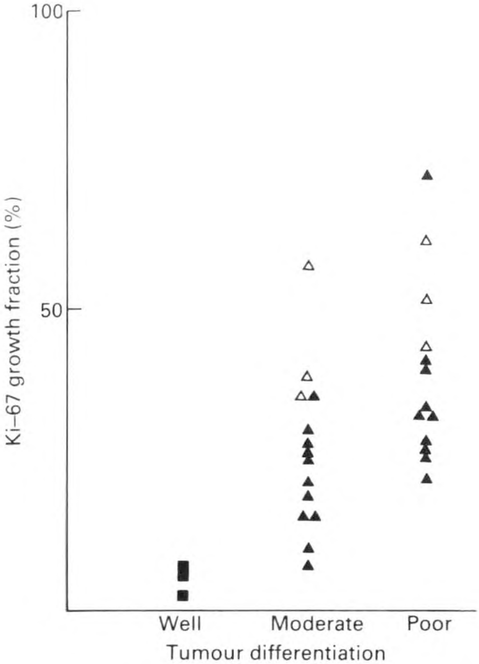

Fig. 2. Growth fractions of 30 ovarian carcinoma determined by immunostaining with Ki-67 on frozen tissue sections; cases were grouped according to their histological grade of malignancy. ■, Clinical stage I; ▲, stage III; △, stage IV. Tumours of high histological grade had higher Ki-67 labelling than tumours of low grade. Differences between the three groups were significant ($P<0·05$).

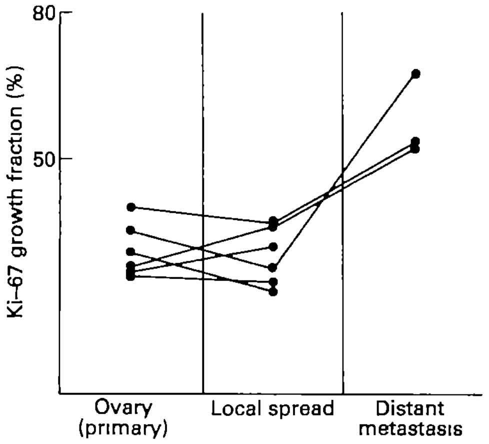

Fig. 3. Growth fraction of six primary ovarian carcinoma with their omental/peritoneal deposits and three metastatic deposits determined by immunostaining with the monoclonal antibody Ki-67. Differences between the primary/adjacent metastases and the distant metastases were significant ($P<0{\cdot}05$)

Ki-67 labelling (growth fraction) in ovarian cancers. This differs from the findings of Brown *et al.* (1988) who reported little or no correlation between the tumour differentiation in cervical carcinoma and the mean percentage value of Ki-67. Other studies are in agreement with our result, reporting that high-grade tumour differentiation had a significantly higher mean value of growth fraction than that in lower grade tumour (Gerdes *et al.* 1986; Gatter *et al.* 1986). As poorly differentiated tumours are generally aggressive and faster growing, a higher growth fraction in these tumours is not surprising. However, we observed a wide variation of growth fraction between patients with the same histological grade. The subjective interpersonal variation in histological grading might offer an explanation for this, or it may be due to the tumour exhibiting variable differentiation at different areas. The growth fraction estimated by Ki-67 in our study appears to reflect more closely the clinical stage of the disease than the degree of tumour differentiation.

There is little published information comparing the growth fraction of a primary tumour and that of its metastases in the same patient. We observed a similar growth fraction in primary ovarian tumour and in adjacent metastases, but distant metastases had a higher growth fraction (Fig. 3). Tubiana (1971) reported that metastatic breast and bronchial cancers grow 1·5–2 times more rapidly than their corresponding primary cancers. As high growth fraction is one of the factors leading to faster tumour growth, our study appears to support their finding. The more rapid proliferation of metastatic tumours may be due to their smaller size in the initial stage of tumour growth repopulation after metastasis, or due to clonal selection.

Several investigators have demonstrated that the growth fraction of a tumour provides valuable prognostic information. The easy applicability of this immunohistochemical labelling method with monoclonal antibody Ki-67 in routine pathology laboratories might enable this variable to be added to the pathological classification and grading, leading to improved treatment selection. Survival was also shown to be significantly correlated with the growth fraction of the tumour, being shorter when the growth fraction is higher. It is unclear at present whether the growth fraction obtained in our study of ovarian cancer reflects the prognosis of patients studied, as the cases have less than 1 year follow-up. Further studies are now in progress to assess the prognostic importance of Ki-67 staining in ovarian cancer.

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Management of tubal pregnancy with methotrexate

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Summary. Ten women with tubal ectopic pregnancy were treated by the injection of methotrexate into the gestational sac under direct laparoscopic vision followed by a course of intramuscular therapy including folinic acid rescue. One course of treatment induced resolution of the extrauterine pregnancy in eight women. Complete resolution (β-hCG<10 miu/ml) was achieved within 6–47 days (mean 14·5 days). Serum β-hCG levels started to decline 3–4 days from the beginning of therapy. Length of hospital stay was 5–11 days (mean 6·4 days). Treatment failed in two patients. One woman had a laparoscopic tubal clip sterilization concomitantly with methotrexate treatment. Tubal patency was demonstrated in all the other seven women (100%) tested subsequently. There is a need to establish criteria for patient selection before methotrexate becomes a routine treatment for tubal pregnancy.

The incidence of ectopic pregnancy has increased during the last decade in spite of worldwide improvement in medical care. The possible main reason has been the concomitant rise in pelvic inflammatory disease (Chavkin 1982). Salpingectomy is the usual method of management.

The development of new diagnostic techniques such as radioimmunoassay of beta human chorionic gonadotrophin (β-hCG), ultrasound and laparoscopy has made early detection of ectopic pregnancy possible (Shapiro 1987). The role of conservative surgery in the management of tubal pregnancy is still under investigation (Lavy *et al.* 1987). We have investigated the use of methotrexate injected under direct laparoscopic vision into the tubal gestational sac followed by a course of parenteral therapy for 5 days.

Subjects and methods

Ten women were studied in the department of gynaecology at the Edith Wolfson Medical Center, Holon, between 30 April 1987 and 1 May 1988. They were told about the risks and benefits of participating in the project. Informed consent was obtained from each patient. Intrauterine pregnancy was excluded by ultrasonography in all the women. Diagnosis was made from the history, physical examination, β-hCG assay, ultrasonography and laparoscopy. Patients were selected if they had a steady or rising β-hCG level, a tubal mass of <4 cm in diameter, intact tubal serosa and no active intra-abdominal bleeding. All the patients were haemodynamically stable and no peritoneal irritation was detected on clinical examination.

At laparoscopy, after identification of the affected tube, methotrexate, 12·5 mg diluted in 1·5 ml of distilled water, was injected into the ectopic pregnancy sac. After 24 h observation, intramuscular methotrexate, 0·5 mg/kg, was administered followed by intramuscular folinic

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Table 1. Protocol for managing tubal pregnancy with methotrexate and folinic acid therapy

Day	Time	Therapy
0	At laparoscopy	Methotrexate, 12 5 mg into the gestational sac
1–5	08·00 hours	Methotrexate, 0·5 mg/kg, intramuscularly
	18·00 hours	Folinic acid, 0·1 mg/kg, intramuscularly

acid, 0·1 mg/kg for 5 days (Table 1). Patients were followed by daily ultrasonography, clinical examination and estimations of haemoglobin concentration, white cell and platelet counts, plasma electrolytes, liver enzymes and kidney function tests. Serum levels of β-hCG were determined on alternate days. When the β-hCG level started to decline the patient was allowed to leave hospital and was followed at the outpatient clinic until β-hCG became undetectable. Hysterosalpingography was performed 1–2 months after resolution of β-hCG levels.

Radioimmunoassay of β*-hCG*

Patient samples, standards and controls were reacted with a mixture of monoclonal antibodies to hCG. Two of the antibodies labelled with 125-iodine attach quickly to unique sites on the hCG molecule and its beta subunit; the third monoclonal antibody, labelled with fluorescein, binds at a discrete site on the hCG beta subunit. At the end of a 15-min incubation at 37°C, sheep antiserum to fluorescein coupled to a magnetic solid phase (MAIA) was added in large excess. This rapidly and specifically binds to the hCG-monoclonal antibody complex, and is sedimented in a magnetic field, eliminating the need for centrifugation. A simple wash step reduced nonspecific binding to a minimum to increase low-end precision. The concentration of antigen was directly proportional to radioactivity bound to the separation reagent. By measuring the bound fraction (separation reagent pellet) of each standard, sample and control in a gamma counter calibrated to detect 125-iodine, the concentration of hCG in the samples and controls can be determined. The hCG MAIA clone standards were obtained from Serono Diagnostics, Switzerland, 0·5 ml per vial, precalibrated to 5, 10, 25, 100, 250 and 500 miu/ml of hCG (1st IRP 75/537) in horse serum with sodium azide, 0·2% (w/v). The detection limit of the assay was <1·0 miu/ml.

Results

The clinical data for the 10 patients are shown in Table 2. The age range was 20–37 years (mean 27·1 years). None had had a previous tubal pregnancy. Gestational age at diagnosis was between 6 and 8 weeks. Small pregnancy sacs were often

Table 2. Clinical and laboratory data of the study group

Patient no.	Age (years)	Gravidity/ parity	Gestational age (weeks)	Site of tubal pregnancy	Size of sac (cm)	hCG level* (miu/ml)	Length of time to resolution (days)	Days in hospital	Tubal patency	Complications
1	25	3/1	7	Left	3	524	8	6	+	—
2**	37	4/3	6	Left	2×3	715	6	6	–	—
3	27	2/1	7–8	Left	3×4	820	15	6	+	—
4	31	4/2	8	Left	1×1·5	3000	47	11	+	Stomatitis
5***	24	2/0	7	Left	3×3	3600	—	—	—	Injection into broad ligament
6***	20	1/0	8–9	Right	3×4	5700	—	—	–	Tubal abortion
7	31	2/1	6	Left	2×3	147	15	5	+	—
8	21	1/0	8	Right	2×3	180	6	5	+	—
9	29	3/2	6–7	Right	2×3	750	9	6	+	—
10	26	1/1	7	Left	1×2	540	10	6	+	—

* Determined on the day of laparoscopy

** The patient has had methotrexate treatment combined with laparoscopic tubal sterilization.

*** Data incomplete because of failure of treatment.

seen. The left tube was involved in seven patients. Serum β-hCG at the time of laparoscopy ranged from 147 to 5700 miu/ml (mean 1597·6 miu/ml). One course of treatment was sufficient to induce resolution of the extra-uterine pregnancy in 8 of the 10 patients studied. Complete resolution (β-hCG<10 miu/ml) was achieved within 6–47 days (mean 14·5 days). Levels of β-hCG usually started to decline 3–4 days from the beginning of therapy. The women spent 5–11 days (mean 6·4 days) in hospital. Only one woman developed stomatitis during treatment.

There were two failures; in both patients β-hCG levels continued to rise. In the first (no. 5, Table 2) this was due to inadvertent injection of the methotrexate into the broad ligament, immediately under the tubal gestational sac. Surgery was undertaken because of a consistent rise of β-hCG levels, and microsurgical techniques were used to preserve the tube. In the second patient (no. 6) laparoscopy revealed an oviduct pregnancy sac measuring 4 cm in diameter and traces of blood in the pouch of Douglas. The concentration of β-hCG was 5700 miu/ml on the day of methotrexate administration and continued to rise during the following days, suggesting a viable pregnancy. The patient started to complain of lower abdominal pains, and signs of peritoneal irritation were found. At laparotomy she was found to have had a tubal miscarriage.

Patient no. 4 has had a hospital stay of 11 days and her β-hCG values did not become negative until the 47th day. A second course of methotrexate was considered but was not given. Another patient (no. 2) had her treatment combined with laparoscopic tubal clip sterilization at her request.

Tubal patency was demonstrated by hysterosalpingography in all the other seven (100%) oviducts. One patient has recently given birth to a healthy female infant.

Discussion

The conservative approach to tubal pregnancy includes expectant and medical management. The first report of a conservative approach to the management of extrauterine gestation was by Lund (1955). The study group was observed until signs and symptoms resolved or surgery became necessary; this was successful in 68 of 119 (57%) patients. The control group had immediate surgery. There were no differences in respect of subsequent fertility and recurrent ectopic pregnancy. The women who were managed conservatively stayed longer in hospital. Tanaka *et al.* (1982) used intramuscular methotrexate to manage interstitial ectopic pregnancy. They confirmed tubal patency following treatment. Later workers administered the drug parenterally and their promising preliminary results have shown the potential of methotrexate as an alternative to surgery (Ichinoe *et al.* 1987; Ory *et al.* 1986; Rodi *et al.* 1986).

Methotrexate was first given locally to an extrauterine tubal pregnancy, transvaginally, under sonographic control (Feichtinger & Kemeter 1987). We used a different approach which includes direct transabdominal injection of methotrexate into the gestational oviduct sac under laparoscopic control followed by intramuscular therapy. Patients managed by intramuscular injections of methotrexate alone tended to stay in hospital longer than those in our study and their β-hCG levels were more persistent (Ichinoe *et al.* 1987; Ory *et al.* 1986; Rodi *et al.* 1986).

Mashiach *et al.* (1982) confirmed the diagnosis of unruptured extrauterine pregnancy by laparoscopy. The patients were followed conservatively by serial measurements of serum β-hCG which became undetectable within a short period of time. We have treated two patients (nos 7 and 8) whose serum β-hCG levels at laparoscopy were only 147 miu/ml and 180 miu/ml respectively. They may not have needed methotrexate, and probably could have been managed safely by serial estimations of β-hCG concentrations. Methotrexate appears to be most effective whenever β-hCG levels are <1000 miu (Ory *et al.* 1986; Ichinoe *et al.* 1987). All our patients who had high β-hCG levels on the day of laparoscopy (nos 4, 5 and 6) had a complicated course.

There has been extensive experience with methotrexate, in gynaecological oncology, in women during the childbearing years, and relatively low rates of side-effects have been reported. There is no evidence that methotrexate is responsible for congenital abnormalities in subsequent pregnancies (Ross 1976; Walden & Bagshawe 1976). It has not been associated with an increased risk of malignancy in later life (Bailin *et al.* 1975), but additional prospective data are needed before a final judgement is made (Klippel & Decker 1985).

Methotrexate is an effective treatment for selected tubal pregnancies; we believe it should be injected directly into the gestational sac, under laparoscopic vision, and be followed by a course of intramuscular injections. Intrauterine pregnancy must be excluded before the start of treatment. There is a need to establish criteria for patient selection, which will include gestational age (Ichinoe *et al.* 1987), the size of the gestation sac (Ory *et al.* 1986), and the β-hCG level on the day of treatment (Ichinoe *et al.* 1987; Rodi *et al.* 1986). Women should be followed by serial β-hCG estimations (Ichinoe *et al.* 1987; Ory *et al.* 1986; Rodi *et al.* 1986) and ultrasound (Ory *et al.* 1986). Methotrexate should not become a routine alternative to surgery until factors such as the dose regimen, morbidity, time in hospital and subsequent tubal function have been fully assessed (Shapiro 1987).

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Warfarin-induced fetal diaphragmatic hernia. Case report

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Case report

A woman aged 20 years developed a deep venous thrombosis in the 7th month of her first pregnancy. She was treated with heparin during the pregnancy and with warfarin after delivery. It was intended to continue the anticoagulant therapy for 1 year. Unfortunately she conceived during this period and used warfarin for the first 14 weeks gestation. She failed to recognize her new pregnancy and did not contact her physician until 12 h before the beginning of labour. Vaginal delivery was uncomplicated but the infant did not breathe and, in spite of attempts at resuscitation, died after 35 min. The infant appeared to be mature, weighed 3660 g and was 48 cm long. The autopsy revealed almost total agenesis of the left diaphragma and hypoplasia of both lungs.

Discussion

Warfarin is the most widely used oral anticoagulant in cardiovascular disease. It is also known to be a teratogen (Hall *et al.* 1980; Ravio *et al.* 1977). The classical fetal warfarin syndrome consists of chondrodysplasia punctata which is characterized by epiphyseal stippling, nasal hypoplasia and relative shortness of the proximal extremities (Hall *et al.* 1980; Ravio *et al.* 1977). The critical period of exposure is supposed to be between 6 and 9 weeks gestation (Hall *et al.* 1980). Exposure outside the first trimester has been shown to carry the risk of central nervous defects (Hall *et al.* 1980; Ravio *et al.* 1977; Briggs *et al.* 1986). Other abnormalities which have been observed are asplenia, spina bifida, absence of clavicles, congenital heart disease and agenesis of the pulmonary artery (Hall *et al.* 1980).

Diaphragmatic malformation is unusual. The incidence is estimated to be 1 per 5000 births (Czeizel & Kovács 1985). Of 237 cases reported from Hungary, agenesis of the left hemidiaphragm without any other malformations, named the Bochdalek type, was observed in 66% (Czeizel & Kovács 1985). Secondary lung complications such as compression and hypoplasia were commonly described.

Review of the reports on warfarin embryopathy revealed only one that suggests an association between warfarin exposure *in utero* and diaphragmatic hernia (O'Donnel *et al.* 1985). This described an infant born to a woman with a renal transplant who had been treated with warfarin as well as prednisone and azathioprine during pregnancy. Our infant with the Bochdalek diaphragmatic hernia is thus the second case that suggests that warfarin taken in the first trimester may induce diaphragmatic malformation. Obviously, the abnormalities may be coincidental, but Czeizel & Kovács (1985) consider that the Bochdalek type is probably most often of teratogenic rather than of genetic origin.

This report provides further evidence that the use of warfarin during pregnancy may result in fetal malformation. Of 463 reported cases of in-utero exposure 25% ended fatally, either in miscarriage, stillbirth or fetal malformation (Briggs *et al.* 1986). Heparin is considered the safest anticoagulant in pregnancy. It does not cross the placenta and theoretically does not affect the fetus (Flessa *et al.* 1965). In spite of a marked maternal complication rate (Hall *et al.* 1980), heparin should be the preferred drug in the very few pregnancies during which an anticoagulant is necessary in the first trimester.

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Single ventricle and pulmonary hypertension. A successful pregnancy. Case report

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Case report

The patient was born in 1964, and a congenital cardiac anomaly was suspected on the basis of persisting cardiac murmurs. There was no cyanosis, and growth and development were normal as was exercise tolerance. Cardiac catheterization was performed at 6 and 9 years of age and suggested a ventricular septal defect. However, in 1974 ventricular angiography was performed and a diagnosis of single ventricle with a 3·4–1 left to right shunt and laevo-transposition of the great arteries was made. Pulmonary hypertension was present at this time. The pulmonary arterial pressure measured 75/40 mmHg (mean 40 mmHg) although the pulmonary vascular resistance was only slightly elevated. Cardiac surgery was discussed, but rejected by her parents in view of her good clinical condition and the high mortality rate related to surgery. Over the next decade mild cyanosis developed and her exercise tolerance diminished.

In 1986 she sought pre-pregnancy advice from her cardiologist and cardiac catheterization was repeated. Systolic pressure in the common ventricle was 110 mmHg. Both aorta and pulmonary artery were entered and had the same systolic pressure as the ventricle. Systemic oxygen saturation was 89% with the patient breathing room air. Calculated systemic blood flow was 3·64 l/min, pulmonary blood flow was 9·53 l/min, systemic vascular resistance 22·8 Wood units (1824 dyne.s.cm^{-5}) and pulmonary vascular resistance 6·08 Wood units (486 dyne.s.cm^{-5}). She was informed about the considerable risks of a pregnancy, and after lengthy discussion she and her husband decided to proceed.

Her first visit to the antenatal clinic was at 13 weeks gestation, following a referral from her general practitioner. She had been admitted previously to the coronary care unit at 12 weeks gestation in atrial fibrillation, and since then had been taking digoxin, 250 µg daily. She was 163 cm in height and weighed 51·5 kg. On examination she had mild central cyanosis; the radial pulse was regular and the rate was 65 beats/min. There was no discrepancy between radial and apical rates. Her blood pressure measured 100/80 mmHg and the jugular venous pressure was elevated to 4 cm. Her apex beat was displaced to the left and was palpable in the anterior axillary line. A thrill was palpable all over the praecordium, and auscultation revealed a 3/6 pansystolic murmur and a 2/4 early diastolic murmur. Her haemoglobin at this time was 14·3 g/dl and the haematocrit was 39·5%.

She was managed as an outpatient in the combined obstetric-cardiological clinic, and remained well throughout the remainder of her pregnancy with no evidence of cardiac decompensation. Serial ultrasound measurement of the fetus showed good growth, and her overall weight gain was 9 kg. Detailed ultrasonography of the fetal heart did not demonstrate any cardiac anomaly.

At 36 weeks gestation she was admitted to the labour ward in early labour. When labour was seen to be established, peripheral arterial and central venous pressure lines were inserted. Epidural analgesia was employed, and electrocardiograph and blood pressure monitoring commenced. A full blood count and biochemistry were normal. Arterial blood gas analysis in room air showed [H+]=37 mmol/l, $P\text{CO}_2$ = 3·9 kPa, [HCO_3^-] = 20 mmol/l and $P\text{O}_2$ =

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7·5 kPa. Antibiotic prophylaxis with ampicillin and gentamycin was commenced. Labour progressed uneventfully, and after a labour of 5 h a live male infant weighing 2630 g was born in good condition by elective low cavity forceps. Oxytocin (10 iu intramuscularly) was given at delivery.

Arterial blood gases, central venous pressure and urine output were monitored for the first 24 h postpartum. After a further 24 h observation her condition was considered stable and she was transferred to the postnatal ward. Five days postpartum she developed increasing dyspnoea and episodes of cyanosis. Arterial blood gas analysis on 3 l/min of oxygen showed $[H^+]$ = 34 mmol/l, $P\text{co}_2$ = 3·7 kPa, $[HCO_3^-]$ = 20·5 mmol/l and $P\text{o}_2$ = 5·6 kPa. Chest infection and pulmonary thromboembolism were excluded, and a diagnosis of pulmonary oedema was made. This was treated with frusemide (40 mg daily) and her condition improved both clinically and biochemically.

She was discharged home 14 days postpartum on digoxin, frusemide, Slow-K and ferrous sulphate. Six months later she remained well and the diuretic had been discontinued

Discussion

Recent improvements in the diagnosis and treatment of congenital heart disease have resulted in an increasing proportion of pregnancies complicated by cardiac disease having a congenital basis (Schaefer *et al.* 1968). Cyanotic congenital heart disease and pulmonary hypertension are both associated with greatly increased maternal mortality—rates of 27 to 50% have been described (Jones & Howitt 1965; Newfeld *et al.* 1974; Gleicher *et al.* 1979), and few cardiologists or obstetricians would advise starting or continuing pregnancy with a risk of this magnitude. It is important to recognize, however, that pulmonary hypertension is heterogeneous: a distinction can be made between dynamic pulmonary hypertension, with an increased pulmonary blood flow and normal or only slightly raised pulmonary vascular resistance, and resistive pulmonary hypertension with a normal pulmonary blood flow and a pulmonary resistance at or above systemic level. Resistive pulmonary hypertension, either as Eisenmenger's syndrome or primary pulmonary hypertension, is associated with a very poor prognosis—even if they surmount the haemodynamic hurdles of increased cardiac output during pregnancy and sudden changes in fluid load and peripheral resistance at the time of delivery, patients can succumb to an inexorable postpartum rise in pulmonary vascular resistance which may relate to thrombotic occlusion of the remaining pulmonary microvasculature. Causes include a greatly reduced pulmonary vascular bed, diminished production of tissue plasminogen activator by pulmonary endothelium, and high levels of pregnancy-related plasminogen activator inhibitor (PAI-2) at the time of delivery.

In contrast, patients with dynamic pulmonary hypertension and a greatly increased pulmonary bloodflow have a much larger pulmonary vascular bed and are less likely to suffer thrombotic complications. On the other hand the increased pulmonary flow coupled with the vasodilatation and fluid retention of pregnancy may lead to congestive cardiac failure and pulmonary oedema. Our patient clearly falls into this latter category, with a pulmonary vascular resistance only slightly above the normal upper limit of 5 Wood units (400 dyne.s.cm^{-5}). In retrospect, the transient postpartum pulmonary congestion may have been partially due to overenthusiastic fluid replacement in an endeavour to maintain an adequate cardiac filling pressure during delivery.

Single ventricle represents only a small proportion of congenital cyanotic heart disease, and only eight other pregnancies complicated by single ventricle have been reported (Table 1). Vaginal delivery with epidural analgesia has been advocated (de Swiet 1984) but caesarean section has commonly been employed in patients with single ventricle (see Table 1), and general anaesthesia used successfully in some of these cases. Oxytocin should be given at delivery in preference to ergometrine. These patients are at an increased risk of premature labour and intrauterine growth retardation (Whittemore *et al.* 1982), thus serial ultrasound growth measurements have been employed. The risk of congenital heart disease in the newborn should be discussed as 16% of infants born to affected mothers will have a cardiac anomaly (Whittemore *et al.* 1982).

The reported cases to date of pregnancies complicated by single ventricle are summarized in Table 1. Of the nine pregnancies two were in the same woman (Leibrandt *et al.* 1982), another ended in miscarriage at 20 weeks associated with maternal death (Mandel & Hirsch 1963), and in

Table 1. Previously published cases of pregnancy complicated by single ventricle

Author	Mode of delivery	Pulmonary hypertension	Maternal outcome	Gestational age (weeks)	Birthweight (g)
Mandel & Hirsch (1963)	Miscarriage	Yes	Died†	20	190
Yuzpe *et al* (1970)	Caesarean section	No	Good	40	2150*
Seeds & Cefalo (1977)	Hysterotomy	No	Good	25	UK (NND)‡
Ahmad *et al.* (1981)	Low-forceps vaginal delivery	No	Good	36	1700*
Leibrandt *et al.* (1982)	Caesarean section	No	Good	40	1520*
"	Caesarean section	No	Good	37	1540*
Stiller *et al.* (1984)	Caesarean section	No	Good	36	2353
Baumann *et al.* (1987)	Caesarean section	No	Good	38	2240*
Present case	Low-forceps vaginal delivery	Yes	Good	36	2630

* Below 10th centile for gestational age.
† The patient died 1 day after miscarriage.
‡ Unknown, neonatal death.

one the pregnancy was terminated by hysterotomy at 25 weeks gestation because of severe maternal haemoptysis (Seeds & Cefalo 1977). Based upon these reported cases, single ventricle is associated with a maternal mortality rate of 11%. Pulmonary hypertension was present in 2 of the 9 pregnancies, including our patient. The previously reported case of single ventricle with pulmonary hypertension resulted in maternal death. Discounting the two losses before 28 weeks gestation, 71% were delivered by caesarean section, preterm labour occurred in 43%, and 71% of infants were small-for-gestational-age. Our patient represents the only reported case of a woman with a single ventricle and pulmonary hypertension to survive pregnancy. The vaginal delivery of a well-grown infant was achieved.

Improved standards of cardiac and obstetric care are, paradoxically, responsible for a dearth of up-to-date information on the outcome of pregnancy in patients with complex, uncorrected congenital heart disease, since most of them are offered elective sterilization or early termination of pregnancy. Increasing numbers of children with congenital lesions are surviving to reproductive age, and with increasing recognition of patient autonomy and responsibility, more are likely to wish to bear children. It is likely that patients with 'dynamic' pulmonary hypertension and a relatively normal pulmonary vascular resistance have a better prognosis than patients with 'resistive' pulmonary hypertension, and this should be taken into account when assessing individual risk.

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Granulosa cell tumour presenting with haemoperitoneum and splenic rupture. Case report

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Case report

An extremely fit 68-year-old nulliparous woman who had not sought medical aid in her entire lifetime had had abdominal distension, dysuria and central abdominal pain for a week and this had become severe immediately before admission. There had been no vaginal bleeding since her menopause at the age of 44. The abdomen was generally tender with a large mass in the left iliac fossa. An abdominal fluid thrill was present. Vaginal examination revealed a large left ovarian tumour. The haemoglobin level was 9·2 g/dl, the white blood count 7·5 × 10^6/dl, and blood coagulation was normal.

At laparotomy the same evening, approximately 1·5 litres of heavily blood-stained fluid was drained from the abdominal cavity, and a left ovarian tumour approximately 14 cm in diameter was removed. Multiple small bleeding points on the peritoneum, omentum and small and large bowel were ligated and a continuous vacuum drain left *in situ*. Because of the marked peritoneal bleeding it was considered prudent not to proceed to hysterectomy and removal of the other ovary, although under more normal conditions this would have been the usual practice in a 68-year-old patient with an ovarian tumour of unknown pathology.

Within 6 h of her return from the operating theatre, evidence of continued intra-abdominal haemorrhage necessitated re-exploration of the abdomen, and a further 1 litre of fresh blood was drained. Three large tears were found in the splenic capsule and a splenectomy was performed. Whilst no further sources of bleeding were noted at this time, it again became obvious within 30 min that intra-abdominal bleeding was continuing, and a third laparotomy was performed. A number of extremely small bleeding points on the pelvic wall were identified and ligated and a large pack was left *in situ* in an attempt to control the bleeding from multiple minute lesions.

Unfortunately, continued bleeding led to a further laparotomy within 12 h at which time the pack was removed, the abdomen drained and corrugated drains left in position.

Up to this time, and throughout admission, all coagulation indices were normal and there was no evidence of disseminated intravascular coagulation. The patient had received 23 units of whole blood and was being mechanically ventilated with 40% oxygen. Her condition remained precarious for a further week during which the volume of blood and sero-sanguinous discharge from the wound gradually tailed off. A further 7 units of blood to compensate for the continuing loss were necessary. Spontaneous respiration was resumed on the fifth postoperative day although she remained unconscious for a further week. In addition she developed bilateral pleural effusions, wound and urinary tract infections and hyperglycaemia, but in spite of these, she was transferred to an ordinary ward within 2 weeks and further progress was uneventful. After a period of convalescence at a local cottage hospital, she returned to her small farm four months later.

The survival after such a hazardous series of events must have been largely due to this lady's extremely healthy pre-operative lifestyle induced by the single-handed management of a small Exmoor farm. Subsequent histological examinations of the ovarian mass showed a solid granulosa cell tumour with a small cystic centre, and the plasma oestradiol on admission was sub-

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sequently found to have been 324 pmol/l which is approximately 10 times the normal postmenopausal level. Splenic section showed no abnormality and the patient denied any pre-admission abdominal trauma, except a slight bump against a chair in church 4 days before admission. As at no time was there any vaginal bleeding it was decided not to proceed with a uterine curettage.

Comment

Granulosa cell tumours make up between 0·6 and 2% of all ovarian neoplasms (Fox & Langley 1976). There is a recognized association between this tumour and haemoperitoneum (Fox & Langley 1976; Novak *et al.* 1971; French 1951) although there are conflicting reports as to the frequency of this association. Very few previous cases have been associated with as large a haemoperitoneum as in our patient (Gondos & Monroe 1971), and an extensive search reveals no similar case. We can also find no publications that show an association between high oestrogen levels and persistent capillary bleeding.

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Detrusor instability associated with menstruation. Case report

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Case report

An 18-year-old nulliparous woman was referred by her general practitioner for investigation of urinary incontinence associated with menstruation for the preceding 2 years. She had occasional nocturnal enuresis and rare incontinence on laughing, but no dysuria or bladder pain. She complained of incontinence by day occurring only during menstruation, but there was otherwise no frequency, urgency or urge incontinence. Her past medical and surgical history was unremarkable. Urinary leakage had been observed and differentiated from menstrual blood by giving the patient phenazopyridine hydrochloride (Pyridium, Warner) to stain the urine orange before menstruation.

Physical examination revealed a healthy young woman. Blood pressure was 120/85 mmHg. Neurological and pelvic examinations were normal. Haemoglobin and serum electrolytes were normal. A micturating cystourethrogram was normal; however, an intravenous urogram revealed a small, irregular left kidney with a deformed calyceal system and loss of renal substance consistent with chronic pyelonephritis. A urine culture grew more than 100 000 colonies/ml of *Klebsiella aerogenes*, and the patient was treated with trimethoprim, 100 mg daily taken at night. A 24-h creatinine clearance was normal at 99 ml/min and a hippuran renogram showed the left kidney contributed only 17% of total renal function, with a normal elimination study.

Urodynamic investigations at mid-cycle showed a maximum free flow rate of 50 ml/s with a total voided volume of 242 ml over 10 s. Subtracted filling cystometry with sterile water in the supine position showed no residual urine, a first desire to void at 210 ml, and a cystometric bladder capacity of 700 ml. There was a mild low compliant detrusor pressure rise to 20 cm H_2O at capacity, but no phasic contractions were noted. Attempts to provoke bladder contractions by standing, coughing, heel bouncing and jogging on the spot were unsuccessful. Stress incontinence was not demonstrated. Urethral pressure measurements, made at rest in the supine position using a Gaeltec transducer catheter orientated in the anterior position, showed a functional length of 3 cm with a maximum urethral closure pressure of 52 cm H_2O. Cystoscopy revealed a normal bladder with slight narrowing of the bladder neck and mild urethritis.

As all these findings were normal and the patient was asymptomatic at the time of testing, she was instructed to return for repeat investigation at the onset of menstruation or symptoms. She subsequently returned with complaints of urgency, urge incontinence, and half-hourly urinary frequency for 24 h coinciding with the onset of her menstrual period. Repeat cystometry at this time showed no residual urine, a first desire to void at 424 ml, and a cystometric capacity of 615 ml. Uninhibited detrusor contractions were produced by filling at a volume of 122 ml in the supine position. Stress incontinence was not demonstrated but, on standing up, the patient had an uninhibited detrusor contraction of 14 cm H_2O which resulted in uncontrolled micturition and she emptied her bladder completely. She was given mefenamic acid, 500 mg thrice daily for 7 days, beginning 3 days before menses, with complete resolution of her symptoms.

Discussion

Although many different disorders have been reported in association with menstruation, the

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association with detrusor instability has not been reported. Although detrusor instability is a common problem in women it is uncommon to find it as closely linked to the menstrual cycle as it was in this patient. We believe that our patient had a low compliant bladder (as represented by her mid-cycle cystometrogram) and developed phasic unstable detrusor contractions with the onset of menstruation. The probable cause for this phenomenon is cyclic prostaglandin synthesis and release.

It is well known that prostaglandins, which often function as smooth muscle stimulants, are synthesized by the endometrium, released at menstruation, and are present in higher concentrations in the menstrual fluid of dysmenorrhoeic women (Pickles *et al.* 1965). Prostaglandins have been shown to enhance the contractility of human and guinea-pig detrusor muscle strips *in vitro* (Bultitude *et al.* 1976; Abrams & Feneley 1976) and to produce similar effects on the human bladder *in vivo* (Desmond *et al.* 1980). Prostaglandin synthetase inhibitors, particularly mefenamic acid, have been found to be effective in relieving dysmenorrhoea and many of the symptoms of premenstrual tension which are thought to arise from excessive endometrial prostaglandin synthesis and release (Anderson *et al.* 1978; Wood & Jakubowicz 1980; Owen 1984). In one controlled trial, flurbiprofen, a prostaglandin synthetase inhibitor, was shown to be clinically useful in the treatment of idiopathic detrusor instability (Cardozo *et al.* 1980). Our patient's rapid response to mefenamic acid therapy during menstruation supports the theory that her urinary symptoms were due to cyclical prostaglandin release affecting a particularly sensitive bladder.

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SHORT COMMUNICATIONS

Factors influencing the uptake of screening for open neural-tube defects and amniocentesis to test for Down's syndrome

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Screening for open neural-tube defects by maternal serum alpha-fetoprotein (AFP) and testing for Down's syndrome by amniocentesis are now routinely available in most obstetric clinics. Although their clinical effectiveness when applied is now established (Cuckle & Wald 1987; Murday & Slack 1985; Weiner *et al.* 1986) little is known about the factors influencing patient uptake. To ensure as far as possible that uptake is the result of informed decisions, more information is needed to determine why eligible women do or do not use these services. Drawing upon several psychological models concerning uptake of health care (for review see Becker & Rosenstock 1984) it was postulated that knowledge about tests and attitudes towards the tests and the pregnancy were predictive of uptake of prenatal screening tests.

Subjects and methods

All women up to 16 weeks gestation presenting for antenatal care to one of three consultants at the Royal Free Hospital between 1 February and 31 May 1986 were eligible for inclusion in the study. Of the 218 women identified 21 women were eligible for amniocentesis to test for Down's syndrome because they were >38 years of age at the expected date of delivery. The remaining 197 were studied for the uptake of serum AFP screening for neural-tube defects.

At the first clinic visit the women see a midwife, and the various tests that may be offered are explained routinely. Serum AFP screening is offered to all women between 16 and 18 weeks gestation; amniocentesis to detect Down's syndrome is offered to eligible women at around the same gestational age. Women return to see an obstetrician 1 week later.

The following information was collected at the first clinic visit.

Knowledge of prenatal tests. This used a standardized questionnaire, giving scores on two subscales: (i) familiarity with test names and (ii) knowledge of the tests used (Marteau *et al.* 1988).

Attitudes towards the current pregnancy and prenatal testing. This used a series of rating scales similar to those developed by Reading *et al.* (1984). These scales included measures of attitudes towards miscarriage of the current pregnancy and attitudes towards amniocentesis.

Attitude towards termination. This was assessed by asking the women whether they would have a termination if the baby had a severe abnormality.

Anxiety. This was measured using a standardized questionnaire developed by Spielberger *et al.* (1970).

Perceived risk of having a baby with an abnormality. This was assessed using an eight-point rating scale, ranging from 0 (not at all likely) to 7 (extremely likely).

Obstetric and demographic details were obtained from the medical notes.

Both groups of women completed all these questionnaires at their first clinic visit when they

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were between 12 and 14 weeks gestation and the 'knowledge questionnaire' was completed again at the second clinic visit.

Results

Of the 197 women eligible for serum AFP screening, 150 underwent the screening, an uptake rate of 76%. Full data were obtained on 161 women. At the first clinic visit women who had the test had better overall knowledge about prenatal tests. By their second clinic visit they differed from those not having the test only in their responses to one item: they were significantly more likely to know the stage of pregnancy at which blood is taken to test for neural-tube defects. They also had a more favourable attitude towards termination of an affected fetus (Table 1).

How much women knew about tests was unrelated to their attitudes towards termination. There were no statistically significant differences between the 'test ' and 'no test' groups in their attitudes towards the pregnancy, perceived risk of having an affected child, anxiety, parity, age, marital status, ethnic origin or social class.

Eleven of the 21 women eligible to have amniocentesis did so, an uptake rate of 52%. Full data were obtained on 18 women. Women who had amniocentesis differed from those who did not in being less concerned about miscarrying the current pregnancy and having a more favourable attitude towards termination of an affected fetus (Table 1). Attitudes towards miscarriage and termination were unrelated. There were no statistically significant differences between the groups in any of the other variables considered.

Comment

These results point to the need to check that all women have adequate information about screening for neural-tube defects, as knowledge is associated with uptake, which is known to vary across clinics (e.g. Bennett *et al.* 1980; Roberts *et al.* 1983; Cuckle & Wald 1987). Some caution is perhaps necessary in the interpretation of these results, given the higher response rate of those who had serum AFP tested. Although lack of information may have led some people not to have the test, having the test is not necessarily

Table 1. Factors associated with uptake of maternal serum alpha-fetoprotein (MS-AFP) screening and amniocentesis

	MS-AFP		Amniocentesis	
Factors	Test (n=128)	No test (n=33)	Test (n=10)	No test (n=8)
Knowledge[‡]				
First visit				
Familiarity with test name	7·5 (1·4)	6·5 (1·7)**	8·7 (0·5)	8·2 (0·4)
Knowledge of tests used	4·0 (1·7)	3·2 (1·7)*	5·1 (1·4)	4·9 (1·3)
Second visit				
Familiarity with test name	8·0 (0·3)	7·5 (1·5)	8·6 (0·5)	8·4 (1·0)
Knowledge of tests used	4·6 (1·5)	4·1 (1·7)	5·7 (1·0)	4·6 (1·4)
Did not know gestational stage of serum AFP screening (n)	24	15**	1	1
Attitudes[†]				
to miscarriage (how bad)	5·9 (1·6)	5·6 (2·1)	5·7 (0·9)	7·0 (0·0)**
to amniocentesis (how good)	3·2 (2·1)	2·1 (1·8)	5·4 (2·4)	1·4 (1·6)*
to termination				
Favourable (n)	105	20	8	1
Unfavourable (n)	23	13**	2	7**

Results are mean (SD) values of scores or numbers of women as appropriate.

Significance of differences between 'test' and 'no test' groups *$P<0{\cdot}05$, **$P<0{\cdot}01$.

[†] Attitudes to miscarriage and amniocentesis were measured on rating scales ranging from 0 (not at all) to 7 (extremely).

[‡] The maximum scores were 9 for familiarity with test name and 6 for knowledge of tests used.

the sign of an informed decision. For example, in a previous study, 29% of women who had serum AFP tested, subsequently denied having had the test (Marteau *et al.* 1988). In contrast, the decision whether to have an amniocentesis seemed to be an informed one. The rate reported here is similar to that reported for other British and American samples (Knott *et al.* 1986; Baird *et al.* 1985). A higher uptake rate of testing for Down's syndrome is unlikely until the risks of miscarriage associated with amniocentesis are reduced yet further, or a non-invasive diagnostic test becomes available.

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Dyspareunia associated with the use of glycerol-impregnated catgut to repair perineal trauma. Report of a 3-year follow-up study

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We have previously reported a randomized controlled trial which compared glycerol-impregnated chromic catgut ('Softgut', soft-catgut-Braun, Davis & Geck Ltd, Gosport, UK) with untreated chromic catgut used for all layers in the repair of perineal trauma (Spencer *et al.* 1986). Women repaired with glycerol-impregnated catgut were more likely to have perineal pain at 10 days and to suffer from dyspareunia 3

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months after delivery. We now report a longer-term follow-up, 3 years after the delivery.

Methods

A three-page postal questionnaire was designed to be sent to the 737 women who participated in the original study. Records held by the Family Practitioner Committee (West Berkshire) were checked for the present address. Approval for this was granted by the Committee Registrar. Questionnaires were sent direct to the women whose addresses were ascertainable in this way. Tracer cards bearing the National Health Service (NHS) number and maiden name of the remaining women were forwarded to the NHS Central Registry. These were returned bearing the code of the Family Practitioner Committee last known to hold these records. The Committees were approached to request the name of each woman's current general practitioner. The general practitioners were then requested to forward the questionnaire to the women.

Results

Overall, 516 (70%) of the 737 women who took part in the original study returned a completed questionnaire. The respondent trial groups were very similar to the original trial groups in respect of descriptive details before suture allocation, later removal of sutures, perineal pain at 10 days and dyspareunia at 3 months (see Spencer *et al.* 1986). Similar data for the respondents are available on request.

A slightly higher proportion of the women who responded in the glycerol-impregnated catgut group had given birth subsequently (44% *vs* 38%—see Table 1). Almost all these deliveries had been vaginal and spontaneous. There was a difference in the frequency with which episiotomy had been performed in first deliveries after the index pregnancy (25% *vs* 14%; P=0·05, χ^2; relative risk 1·8, 95% CI 1·0 to 3·3), although this was not reflected in an increase in the overall frequency of perineal suturing (relative risk 1·0, 95% CI 0·9 to 1·2).

Table 1. Results of 3-year follow-up

	Allocated group	
Variable	Softgut	Catgut
No. women in original trial	377	360
No. women who replied to questionnaire	263	253
Babies born since study *n* (% respondents)		
0	147 (56)	156 (62)
1	109 (41)	94 (37)
2	7 (3)	3 (1)
Management of first subsequent delivery *n* (%)		
Mode of delivery		
Spontaneous vaginal	111 (96)	94 (97)
Instrumental	3 (3)	1 (1)
Caesarean section	2 (2)	2 (2)
Episiotomy performed *n* (% vaginal deliveries)	28 (25)	13 (14)*
Perineum sutured *n* (% vaginal deliveries)	82 (72)	69 (73)
Sexual intercourse painful *n* (% respondents)	51 (19)	29 (11)**
Soreness	43	28
Tightness	2	0
Other	6	1
Subanalysis based on women with no subsequent deliveries		
Sexual intercourse painful *n* (%)	28/146 (19)	15/155 (11)***
Soreness	23	14
Tightness	1	0
Other	4	1

* χ^2 (1 d.f.) = 3·89; P=0·05.

** χ^2 (1 d.f.) = 6·18; P<0·02.

*** χ^2 (1 d.f.) = 5·54; P<0·02.

Sexual intercourse was reported as painful 1·7 (95% CI 1·1 to 2·6) times more often by women repaired with glycerol-impregnated catgut ($P<0{\cdot}02$, χ^2), even when the analysis was limited to women who had no subsequent deliveries (Table 1). In an open question, most women described the dyspareunia as 'soreness'.

Discussion

This study suggests that glycerol-impregnated chromic catgut causes persisting dyspareunia, and it may also increase the likelihood of episiotomy during subsequent delivery. Three years after the index perineal repair, as many as 8% of women reported dyspareunia which could be attributed to its use, regardless of whether or not there had been subsequent deliveries. Equal amounts of material were used for the repair in the two groups (Spencer *et al.* 1986). Although significantly more women in the untreated catgut group had some suture material removed in the 3 months following the index delivery, this difference is not sufficient to explain the contrast in perineal pain at 10 days, dyspareunia at 3 months, and persistent dyspareunia at 3 years. Another possible explanation is differences in the chromic catgut of the two products. The speed of absorption is related to the chromium concentration and the tissue reaction to the quality of the raw material (Madsen 1953). Although glycerol impregnation appears not to alter the immediate inflammatory reaction (Stone *et al.* 1985), the most likely explanation is that the perineal tissues reacted differently to the glycerol-impregnated catgut, possibly with increased fibrosis. Judged on this trial there is no place for glycerol-impregnated chromic catgut in the repair of perineal wounds.

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Should follow-up be provided after miscarriage?

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Miscarriage is a very common event (Huisjes 1984), but although recently much attention has been paid to the effects of recurrent miscarriage (Beer 1986), little has been written about the needs of women suffering sporadic miscarriage.

To assess the possible need for a follow-up service after miscarriage, women admitted to Glasgow Royal Infirmary with bleeding in the first trimester of pregnancy were scanned by the researcher. Where the pregnancy was not continuing, the woman was subsequently asked if she wished to take part in a study on miscarriage. All the 72 women approached agreed to co-operate, and a structured interview covering

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Table 1. Prevalence of abnormal symptoms complained of by 42 women attending follow-up after miscarriage

Symptom	Initially	At follow-up
Tiredness	32 (76%)	12 (29%)
Irritability	24 (57%)	7 (17%)
Tearfulness	39 (93%)	21 (50%)
Difficulty in sleeping	16 (38%)	1 (2%)
Loss of appetite	11 (26%)	2 (5%)

social, medical and obstetric details was completed. The women were then offered a follow-up appointment 6 weeks later and were told how to contact the researcher should they wish to do so although 15 women felt that they did not wish to return. At follow-up an open-ended interview covered a wide range of feelings, attitudes and physical reactions to the miscarriage.

Results

Of the 57 women who had a follow-up appointment, 42 attended (74%). Four of the 25 childless women (16%) declined follow-up compared with 26 of 47 women with children (55%). Apart from age (attenders mean age 32 years, non-attenders mean age 27 years, $P<0.0005$) there were no demonstrable differences between the groups. None had undergone infertility investigations.

The 42 women who were interviewed again after their miscarriage reported a number of symptoms suggestive of depression, which were resolving with time. These symptoms were judged by the women to be abnormal for them (Table 1).

All the women had found it hard to grieve for someone who had 'never existed' and frequently felt that they were 'going mad' to feel the way they did. Feelings of guilt were still very common with 64% experiencing marked guilt. Most women had generalized guilt feelings and seemed to benefit by being told that it was unlikely that any action of theirs had caused the miscarriage. Although most women wished to discuss the loss, 16 (38%) felt that they coped better by keeping their feelings to themselves. Although 32 women (76%) reported that their families and friends had been fairly supportive the other 10 felt that they had had no-one to talk to and that their husbands were 'totally lacking in understanding'. Nine of the 23 women in employment had not felt ready to return by the time of the interview.

Of the 42 women interviewed 21% complained of their medical care; they had felt unprepared for the diagnosis of miscarriage, and the way in which this was communicated had seemed brusque. Six women were upset with their general practitioner because of delays in referral to hospital.

Although detailed verbal explanations were given to all women in hospital by the researcher, only 17 (40%) of those at follow-up recalled any of this information.

Most of the women remembered the events of the miscarriage clearly and found the need to go over these in great detail; being given an opportunity to talk this through was helpful. They also appeared to be comforted by the knowledge that their reactions were normal and by being given permission to grieve. All the women who attended follow-up commented that they had found the interview very helpful and several asked for further visits.

Thirty-nine (93%) women followed up were anxious about future pregnancies. Thirteen of the 42 women followed up contacted the researcher when they became pregnant again; eight showed considerable anxiety and requested frequent ultrasound scans until early in the second trimester when their confidence improved.

This study suggests that some women will benefit from help and support after a miscarriage and in future pregnancies. A follow-up service should be available to all women experiencing miscarriage, recognizing that it will not be universally required. Printed information, which can be taken home at the time of discharge, can supplement the value of the usual verbal explanation.

Acknowledgments

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Gemeprost vaginal pessaries for inducing third-trimester intrauterine deaths

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The prostaglandin analogue, 16,16-dimethyl-trans-Δ^2 prostaglandin E_1 methyl ester (gemeprost), was initially marketed in pessary form for cervical softening prior to first-trimester termination of pregnancy. Subsequently it has been used for second-trimester terminations (Sakamoto *et al.* 1982), and has been shown to be as effective as extra-amniotic prostaglandin E_2 (PGE_2) (Cameron & Baird 1984). We describe its use in inducing labour after third-trimester intrauterine death in 10 women.

Patients, methods, and results

On admission to the labour ward, an assessment was made of the cervix, and the Bishop score was recorded. A 1-mg gemeprost pessary was then inserted into the posterior fornix of the vagina; this was repeated every 4 h if necessary. When the cervix was fully effaced with bulging membranes, amniotomy was performed. Mean gestational age was 34·3 weeks (SD 3·1), four patients were nulliparous. Mean admission Bishop score was 1·9 and the mean number of pessaries used 1·9 (SD 0·7). The mean duration of labour was 11·7 h (SD 4·6), and the mean length of the active phase of the first stage of labour 1·65 h (SD 0·8). The mean blood loss was 139 ml (SD 85 ml). No patient required additional oxytocin.

The results are detailed in Table 1.

The patients were mobile during most of the procedure and were able to relax or move about as they wished. Opiate analgesia was used or an epidural was inserted towards the latter stages at the patient's request. The only side-effects noted were mild pyrexia in eight patients and diarrhoea in two.

Comment

The death of a fetus in the third trimester of pregnancy is an unpleasant event for any woman, and for this and medical indications prompt delivery is advisable. If the cervix is favourable then this can be accomplished with conventional induction agents. For the unfavourable cervix these are less successful and other regimens have been employed. These include PGE_2 administered intravenously, via the intra- or extra-amniotic route or vaginally (Southern *et al.* 1978), and synthetic agents such as 15(S)-methyl $PGF_{2\alpha}$ intramuscularly (Wallenburg *et al.* 1980). These and other methods are reviewed by Ratnam & Prasad (1986) and all are less than ideal in practice. Vaginal PGE_2 requires large frequent doses whilst some preparations are unavailable commercially. Extra-amniotic instillation limits the patient's mobility and requires skilled placement of the catheter, whilst other methods are hazardous, painful or otherwise distressing to the patient. Gemeprost appeared to be effective and acceptable in inducing labour in the 10 women in our study. The mean induction–delivery time was 11·7 h, comparable with vaginal PGE_2 (10·7 h) and 15(S)-methyl $PGF_{2\alpha}$ intramuscularly (10·4 h primiparae, 7·3 h multiparae). The mean number of administrations was, however, considerably reduced, the comparable figures being 1·9 (range 1–3), 3 (range 1–10) and 5 (range 3–28). Of note was the short active phase of the

Table 1. Details of the 10 women in the study

Patient no.	Age (years)	Parity	Gestation (weeks)	Bishop score	No. of pessaries	Induction–delivery interval (h)	Fetal weight (g)	Blood loss (ml)
1	27	G3P2	30	1	3	19	1550	250
2	35	G3P2	41	4	2	16	3200	150
3	28	G4P3	33	UK	2	14	1850	100
4	25	G2P1	31	UK	1	7	370	180
5	19	G1P0	35	2	2	10	1410	50
6	20	G2P0	32	1	2	10	1050	50
7	26	G3P2	35	1	2	17	2120	150
8	32	G9P7	34	3	1	6	2980	100
9	26	G1P0	36	1	3	11	1540	60
10	29	G2P0	36	2	1	7	2240	300

UK, Unknown.

first stage of labour in the patients treated with gemeprost. All prostaglandins have well-reported side-effects, which in some cases limit their use. Pyrexia, diarrhoea and vomiting are particularly common, each occurring in 40–50% of women given vaginal PGE_2 in the above series. Although 8 of our 10 patients developed a pyrexia, this was not serious, and settled quickly on delivery. Two women had diarrhoea, but no other side-effects were noted. In this study gemeprost was found to be an acceptable, efficient, readily available and easy to administer agent in inducing labour in third-trimester pregnancies complicated by intrauterine death. We believe it to be worthy of further study.

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Low-dose follicle-stimulating hormone in the treatment of polycystic ovary syndrome: a comparison of pulsatile subcutaneous with daily intramuscular therapy

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Polson *et al.* (1987) found that treatment with

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Table 1. Results of treatment with low-dose follicle-stimulating hormone (FSH)

	Pulsatile subcutaneous (n=15)	Intramuscular (n=14)
No. of treatment cycles	51	34
No. of cycles per patient Median (range)	3 (1–8)	2 (1–6)
No. of ovulatory cycles	40 (78%)	23 (68%)
No. of uni-ovulatory cycles	22	15
No. of pregnancies	6	6
FSH dose		
Maximum daily dose (units) (Mean (SD)	123 (43)	115 (32)
Total dose (ampoules) Median (range)	24 (8–65)	16 (7–34)*

*$P<0.05$, Mann–Whitney U-test.

low-dose pulsatile follicle-stimulating hormone (FSH) resulted in a high rate of ovulation of a single dominant follicle, but it is not clear whether the success of treatment was related to the pulsatile mode of administration or to the low dose of FSH used. Because it is obviously more convenient to give a single daily dose of FSH than to deliver the hormone by a pulsatile infusion pump we undertook a study to compare the efficacy of treatment using these two routes of administration.

Subjects and methods

The study included 29 women with anovulation related to polycystic ovary syndrome; 26 of them had oligomenorrhoea, three had amenorrhoea and 18 had clinical evidence of androgen excess, hirsutism or acne or both. Each had polycystic ovaries on ultrasound (Adams *et al.* 1985, 1986) and at least one biochemical abnormality (raised serum LH, testosterone or androstenedione) characteristic of the syndrome. All had failed to ovulate in response to at least three successive courses of clomiphene. This was a non-randomized study but one in which the treatments were administered over a similar period by the same investigators. Patients with tubal or male infertility factors were excluded from the study with the exception of a single subject in the subcutaneous treatment group who was found to have a persistently negative post-coital test during treatment although her husband's semen analyses had been within normal limits.

The regimen for administration of low-dose FSH was essentially that described by Polson *et al.* (1987). Briefly, FSH (urofollitrophin, Metrodin, Serono, UK) was given either at 90-min intervals subcutaneously by means of a portable pulsatile infusion pump or by daily intramuscular injection. In either case the starting dose was 75 units/day. This dose was maintained for at least 7 (usually 10–14) days and thereafter increased in a stepwise fashion by 37·5 units if there was no evidence of follicle maturation. Once a dominant follicle (diameter ≥12 mm) emerged, the dose was maintained until the lead follicle was >16 mm, at which point hCG, 3000 iu intramuscularly, was given.

Results and comment

Of the 29 women 15 received FSH subcutaneously (subcutaneous group) and 14 intramuscularly (intramuscular group). The median (range) duration of infertility was similar in the two groups: subcutaneous 6·3 (2–16) *vs* intramuscular 5·4 (2–12) years. There were no significant differences between the groups (subcutaneous *vs* intramuscular) in the mean (SD) age of the subjects: 31(5) *vs* 29(3) years; body-mass index (kg/m^2): 24·0 (3·8) *vs* 24·1 (4·1); baseline serum LH: 17 (8·9) *vs* 14·8 (9·2) units/l; testosterone: 3·5 (1·7) *vs* 3·8 (0·9) nmol/l; androstenedione: 9·0 (4·2) *vs* 9·1 (6·3) nmol/l.

The outcome of treatment is summarized in Table 1. Overall, 74% of the total cycles were ovulatory but only two subjects (one in each group) failed to ovulate in at least one cycle of treatment. There were no significant differences between subcutaneous and intramuscular administration in the number of ovulatory cycles, the number of single ovulations or the rate of pregnancy. The total dose of FSH required was slightly greater in the subcutaneous group than in the intramuscular group (23·6 *vs* 15·7 ampoules) but the mean maximum dose of FSH required was similar (123 *vs* 115 units/day). In uni-ovulatory cycles, mean concentrations of oestradiol on the day of hCG were similar in the two groups (subcutaneous 1330 *vs* intramuscular 1482 pmol/l) as were the mid-luteal progesterone concentrations (56 *vs* 67 nmol/l). Of the 12 pregnancies there was one twin pregnancy in each group, two early miscarriages (within 6 weeks of ovulation) in the subcutaneous group and one in the intramuscular group. The remaining pregnancies progressed successfully to term.

Although this was not a randomized study the two groups of women were well matched, and in the event there were no significant differences between them in the outcome of treatment. In both groups there was a satisfactory rate of ovulation with a high percentage of uni-ovulatory cycles. The overall pregnancy rate was 41% (12 of 29) with a low rate of multiple pregnancy. These data confirm the efficacy of low-dose FSH treatment in anovulatory women with polycystic ovary syndrome (Yen 1980; Kamrava *et al.* 1982; Polson *et al.* 1987), particularly with regard to the low rate of multiple pregnancy, but show no difference between pulsatile subcutaneous or daily intramuscular injection. The latter is therefore a satisfactory and convenient form of administration. This study does not address the question of whether 'pure' FSH in low dosage has any advantage over low-dose human menopausal gonadotrophin (hMG). Our initial studies using pulsatile hMG suggest that this is equally effective (Franks *et al.* 1987) but a prospective controlled study comparing intramuscular FSH with hMG is in progress.

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CORRESPONDENCE

Retrieval of intrauterine contraceptive devices with missing tails, using Lamicel

Dear Sir,

We are pleased that Professor Akerlund [*Br J Obstet Gynaecol* (1989) **96,** 254] found our writing (Johnson & Moodley 1988) colourful, but we are disappointed that he has missed the point of our paper. We accept that thread retrievers, such as the 'Retrievette', can be used to recover lost loops but in our paper we described patients in whom a thread retriever had already been used and failed. They were tertiary referrals from family planning clinics, where initial attempts to remove the lost coil had been made. As is clear from the text, a further attempt was made with a thread retriever or fine forceps in all of these patients. It was successful in 11 women out of 47, a further five were excluded for other reasons, leaving the 31 patients we described.

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Johnson N. & Moodley J. (1988) Retrieval of intrauterine contraceptive devices with missing tails, using Lamicel. *Br J Obstet Gynaecol* **95,** 97-100.

Dear Sir,

Professor Akerlund [*Br J Obstet Gynaecol* (1989) **96,** 254], commenting on a technique described by Johnson & Moodley (1988), advocates the use of thread retrievers such as the 'Retrievette'. However, the problem with such devices is that they have to rely on the thread for removal of the IUCD. This reduces the reliability of the procedure, and most reports quote a success rate of 50% (Chamberlain 1982) or less. A recent series (Gardosi 1988) reported that in about 40% of cases the 'missing thread' was found to be wound around the stem of the IUCD or stuck to it with blood and mucus. Other threads are cut too short, or become too short for retrieval when the device rotates, or avulse after reduction in tensile strength (Bromham 1982) and after embedding of the IUCD.

An alternative outpatient method to the use of thread retrievers or cervical dilatation with Lamicel is to use the new IUCD forceps (Rocket R 29091 or Zeppelin 16868 GY), a thin flexible forceps designed to grasp the 'lost' IUCD directly. This method is quick and reliable, and successful removal was achieved in 91% of all referred cases of an initial series of 45 patients (Gardosi 1988); since then the total number has risen to 68 with a retrieval rate consistently over 90%. In well over half these patients, one or more unsuccessful attempts at removal with thread retrievers had been made before referral.

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The distribution of CA125 in the reproductive tract of pregnant and non-pregnant women

Dear Sir,

I read with interest the paper by Jacobs *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 1190–1194] on the distribution of CA125 in the female reproductive tract. These results confirm our previous findings of large amounts of CA125 in the cytosols of normal endometrium and tissue of a miscarriage (Fuith 1987).

However, the authors failed to explain the mechanisms by which CA125 gains access to the maternal circulation during pregnancy.

The paradox of high levels of CA125 in certain tissues and body fluids and low serum levels is well known. For ovarian tumours the antigen may leak into the circulation only from infiltrative growth (Fleuren *et al.* 1987). A similar situation seems to exist in early pregnancy when the trophoblast invades the decidua and the uterine veins (Bigelow 1982). CA125 probably enters the maternal circulation from the invading tissue. This is substantiated by the fact that Jacobs *et al.* and other workers (Halila *et al.* 1986; Niloff *et al.* 1984) report CA125 elevations in the serum only during the first trimester of pregnancy.

However, a second rise of CA125 levels has been observed during and immediately after delivery (Itahashi *et al.* 1988). This is probably a result of an antigen transfer occurring during the placental separation.

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Endometrioid carcinoma of the ovary: a retrospective study

Dear Sir,

I read with interest the paper by Tidy & Mason [*Br J Obstet Gynaecol* (1988) **95**, 1165–1169] on endometrioid carcinoma of the ovary and would like to make the following comments.

Endometrioid carcinoma of the ovary has been cited to be the histological subtype of ovarian carcinoma most often associated with adenocarcinoma involving the endometrium (Czernobilsky *et al.* 1972; Zaino *et al.* 1984). Like others (Rose *et al.* 1987), we (Piura & Glezerman 1989) could not confirm this observation. In five patients with synchronous carcinomas of the endometrium and ovary we found that all uterine cancers were typical endometrial adenocarcinomas while four of the ovarian cancers were serous papillary cystadenocarcinomas and only one was an endometrioid carcinoma.

I agree with the authors that a patient presenting with synchronous carcinomas of the ovary and endometrium poses a diagnostic dilemma. If different histological subtypes are present in the ovary and endometrium then one may assume the coexistence of two primary tumours, but if both ovary and endometrium harbour the same histological subtype of malignancy no definite decision can be made as to whether a single metastatic tumour or two separate primary tumours are present. Accumulating experience (Czernobilsky *et al.* 1972; Eifel *et al.* 1982; Zaino *et al.* 1984; Rose *et al.* 1987; Piura & Glezerman 1989) indicates a surprisingly good survival rate in patients with synchronous carcinomas of ovary and endometrium, even and especially if endometrioid carcinoma of the ovary is associated with typical adenocarcinoma of the endometrium, unless the endometrial cancer invades deeply into the myometrium.

It is suggested (Piura & Glezerman 1989) that when both ovarian and endometrial carcinomas are confined within the limits of their tissue of origin without evidence of spread into adjacent tissues or organs, they should be considered as separately and synchronously occurring two low-stage primaries, and surgery may be less aggressive. This is true regardless of whether the carcinomas are of the same or of different histological subtypes. When there is evidence that at least one tumour is spreading to adjacent tissues and organs the question of two separate primaries or one metastatic tumour becomes academic, and aggressive surgical treatment with adjuvant chemotherapy, radiotherapy, or both, is indicated.

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Alternative vacuum supplies for ventouse deliveries

Dear Sir,

In a recent short communication Constantine *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 249–250] correctly stated that one of the reasons why the ventouse was not popular in this country was the fact that the equipment was often poorly maintained leading to frequent failure of delivery. They also cited conservatism among many doctors. Could I suggest that prejudice among midwives is also an important factor, particularly where the old familiar handpump is employed (usually worked by a midwife).

Constantine and his colleagues describe the use of either the hospital piped vacuum supply, with a suitable pressure reduction valve, or a portable anaesthetic suction machine to develop the required vacuum. They do, however, note that these machines are often calibrated in a confusing variety of units.

I would therefore like to suggest a method which I have used previously with some success. This is to connect the vacuum supply, from a portable anaesthetic suction machine, to the original glass bottle of the ventouse apparatus instead of the handpump. This method obviates the need to purchase a special plug-in reducing and control valve and allows the vacuum to be regulated by the valve on the bottle. The vacuum can be read off from the gauge on the bottle, calibrated in familiar units.

I have found this method quite satisfactory, when working in units which did not possess a dedicated electric ventouse vacuum pump.

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Dear Sir,

With reference to the short report by Constantine *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 249–250], I would like to support the view of the authors that the use of piped vacuum supply, as moderated by equipment to provide oropharyngeal suction, is a safe method of providing suction for ventouse delivery. This method has been in use at our hospital for at least 6 years and I have personally carried out 14 such deliveries from the occipito-lateral position using this method with Malmstrom cups with no significant fetal morbidity.

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Vaginal cones: a conservative method of treating genuine stress incontinence

Dear Sir,

We should like to congratulate Peattie *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 1049–1053] on their paper on vaginal cones. We consider that this may be an important development in conservative therapy and therefore needs to be thoroughly assessed before widespread usage.

The authors claim a 90% acceptability and yet they had a drop-out rate of 23%. Such overstatements do not assist in the promotion of a new technique, no matter how promising it is. The fact that only 13 of 39 patients continued with the therapy and maintained their improvement argues for an acceptability of 33%. Such a low rate could be a placebo effect.

It has been stated that the bladder is an unreliable witness, in that subjective assessment can be misleading. For this reason an objective method is necessary. The authors have employed a standardized 1-h pad test as their only objective measure and yet the sensitivity and reproducibility of this has been questioned (Versi *et al.* 1988; Jakobsen *et al.* 1987) with the test–retest differences having a variation of up to 24 g (Lose *et al.* 1988). Examining the objective effects of vaginal cones, Peattie *et al.* found that 8 patients had been cured, 8 had got worse, 14 had improved and 9 had dropped out. Given the variability of the pad test employed, should these results be taken to show objective improvement?

The authors suggest that the reduction in incontinence is related to the increase in retained cone weight. To this end they have presented an analysis of Spearman's rank correlation comparing the change in cone weight with the change in pad weight (Table 2, p. 1052). They have obtained correlation coefficients of $-0{\cdot}21$ and $-0{\cdot}827$ for their two groups, which are said to be statistically highly significant. In fact a value of $-0{\cdot}21$ is not significant and our analysis of their data yields Spearman's rank correlation coefficients of $-0{\cdot}21$ and $-0{\cdot}29$, both of which are not significant. Scatter plot analysis reveals no trends, casting doubt on the presence of any relation between the improved ability to retain vaginal cones and decreased incontinence.

All the patients in the study were premenopausal and it has been claimed that the severity of incontinence can be affected by the menstrual cycle. There is no indication that the authors have controlled for this potential variable.

The authors place great emphasis on the difference between active contraction of the pelvic musculature and passive tone. However, it is not clear how they were able to ensure that the 'passive' cone results were obtained in the absence of active contractions. The fact that after treatment the passive cone weight and the active cone weight were the same in 50% of patients, and that there was a highly significant correlation between change in 'passive' cones and change in 'active' cones (Spearman's rank correlation coefficient: $r = +0{\cdot}89$, $P<0{\cdot}01$), suggests that this arbitrary differentiation serves no useful purpose.

The duration of this study was only 1 month. This is a relatively short time in which to rehabilitate pelvic floor musculature. It could be argued that a longer study period could have produced less disappointing results and would have promoted this new therapy more realistically.

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Authors' reply

Dear Sir,

We are grateful to Dr Versi and Ms Mantle for their careful reading of our paper and would like to answer their points as follows.

We use the term acceptability to mean that this was a technique which the patients were happy to use. Our figure of 90% was derived from the 30 patients who completed 1 month of training and were then asked for their views. The technique was applied to patients already counselled for and expecting incontinence surgery, so to show one-third prepared to continue exercises at the end of treatment is very encouraging. Based on the pilot study which we have published we now feel justified in continuing a more detailed long-term assessment of this technique.

We are grateful to Dr Versi for correctly pointing out that we have miscalculated the Spearman's rank correlation coefficients comparing the change in pad weight with the change in cone weight. The result is thus disappointing but the fact remains that a significant correlation still exists between the improvement in incontinence and the patients' appreciation of benefit from the course of exercises. As the correspondents point out, this improvement is noted after a mere month of exercise so, as they rightly suggest, a longer study period may produce a more rewarding result.

As for using the standardized 1-h pad test as one of the outcome measures, this has been a point of debate at most International Continence Society meetings, as Dr Versi is well aware. We should be happy to replace this with a more reproducible objective measure of incontinence, should Dr Versi be able to suggest one. He quotes a paper where he compares the pad test with videocystourethrography (VCU) which is an objective but non-quantitative method of demonstrating incontinence and is thus not applicable here. VCU also subjects the patients to irradiation and requires catheterization for each test.

A comparison of the passive and active cone weights before and after treatment shows a highly significant improvement in the ability to hold a heavier weight after treatment. We hope that further studies may show the objective improvement in incontinence that this study shows the patients feel subjectively.

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Complete response to pre-operative chemotherapy in stage III B cervical carcinoma. Case report

Dear Sir,

The complete response to chemotherapy in the patient described by Benedetti Panici *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 946–948] led them to conclude that pre-operative chemotherapy could be of considerable advantage in patients with advanced carcinoma of the cervix.

The tumour was said to be 'squamous cell carcinoma of the small-cell poorly differentiated type', although a photomicrograph was not included in the article.

Small-cell tumours have been increasingly described in extrapulmonary sites (Ibrahim *et al.* 1984) and were first described in the cervix by Field *et al.* (1964). It appears likely that they are derived from neuroendocrine APUD cells and differ from squamous carcinoma in histogenesis, biological behaviour and response to therapy (Mackay *et al.* 1979).

Correct diagnosis of small-cell carcinoma is very important as, at least in the lung, it shows significant sensitivity to certain regimens of cytotoxic therapy (Editorial 1979). Unfortunately two reported cases of cervical small-cell carcinoma treated in part by chemotherapy have failed to show any response (Jones *et al.* 1976; Johannessen *et al.* 1980).

Single-agent chemotherapy for advanced or recurrent carcinoma of the cervix using doxorubicin, cyclophosphamide, 5-fluorouracil, bleomycin, methotrexate or mitomycin C has shown response rates of between 10 and 28% although this increased to 24–50% in selected patients treated with cisplatin (Muscato *et al.* 1982). Combination regimens have shown no benefit over cisplatin alone.

Small-cell carcinoma of the cervix is rare, accounting for only six of 3507 malignant neoplasms of the cervix reviewed by Albores-Saavedra *et al.* (1976). Professor Benedetti Panici's report of complete response in a patient with small-cell poorly differentiated carcinoma of the cervix is the first reported complete response to chemotherapy and is therefore encouraging for those 0·17% of patients with this rare tumour, although any advantage to those patients with advanced squamous-cell carcinoma of the cervix must remain in doubt.

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Authors' reply

Dear Sir,

We thank Dr Divers for his comments on our case report. Our patient was reported to have a small-cell poorly differentiated *squamous* carcinoma. Our pathologists currently classify cervical squamous carcinomas according to the predominant cell type (large-cell keratinizing, large-cell non-keratinizing, and small-cell non-keratinizing) (Reagan & Ng 1973), and degree of differentiation (well-differentiated, moderately well-differentiated and poorly differentiated). In the poorly differentiated 'oat cell' variety of neuroendocrine carcinomas of the cervix—this is the topic of Dr Divers' letter—foci of squamous differentiation are occasionally seen only in the well-differentiated types. Furthermore, Grimelius staining or electron microscopy should demonstrate the presence of argyrophile neurosecretory granules, even though none of the reported cases has been associated with the carcinoid syndrome.

In our patient the presence of foci of squamous differentiation excluded a neuroendocrine origin, so that Dr Divers' remarks seem to be inappropriate.

In our experience, preliminary results suggest that pre-operative chemotherapy has some value in locally advanced cervical carcinoma (Benedetti Panici *et al.* 1988). This is why a randomized trial of pre-operative chemotherapy followed by radical surgery versus conventional radiotherapy has just been undertaken in collaboration with the Istituto Nazionale Tumori of Milan.

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BOOK REVIEWS

A Practical Guide to Labour Management by Donald Gibb. Blackwell Scientific Publications, Oxford, 1988, 152 pages with figures and tables, £9.50

Here is an excellent attempt to provide a straightforward text for use by those (mainly SHO grade) doctors who are being faced with management decisions on the labour suite for the first time. Any book as short as this is by nature didactic and inevitably there are statements which are open to argument, but I did not find any which were not entirely reasonable recommendations in line with mainstream obstetrics. Moreover, the fine line between safety and over-intervention is well drawn for most of the book, with a clear (though perhaps understated) respect for the emotional needs of the labouring woman as well as the simply mechanistic requirements of care in labour.

While to some extent the emphasis reflects Donald Gibb's research interests, particularly in his treatment of the use of oxytocin, fetal heart rate trace interpretation and uterine contraction monitoring, he has achieved an admirably balanced view of intrapartum care of mother and baby. This is complemented by a chapter on neonatal care contributed by Dr Anne Greenough, which is brief to the point of terseness but lists the areas of knowledge required for adequate perinatal care.

This is the first book that I have come across which fills the gap between undergraduate obstetric teaching aimed at a general understanding of the concepts of obstetrics and the subtle clinical skill of judgement applied to labour and delivery. It is probably a little simplistic for the MRCOG candidate, but I will be recommending it to all those doctors who are appointed to the SHO obstetric posts at Bristol Maternity Hospital as a valuable guide to assessment and management in the difficult weeks of learning which follow 1 February and 1 August.

Ken Bidgood

The Onset of Labor: Cellular and Integrative Mechanisms (Reproductive and Perinatal Medicine (IX) A National Institute of Child Health and Human Development Research Planning Workshop Bethesda 1987) edited by D. McNellis, J. R. G. Challis, P. M. MacDonald, P. W. Nathanielisz & J. M. Roberts. Perinatology Press, Ithaca, 1988, US $57.50 (list price $68.50)

This book presents the proceedings of a research conference organized by the National Institute of Child Health and Human Development in Bethesda, Maryland, in December 1987. The purpose of the conference was to delineate the research priorities in human parturition to provide a basis for the prevention of preterm labour. The book has two introductory chapters, by Mont Liggins and Howard Rasmussen, eight chapters on myometrial regulation, three on the roles of placenta and fetal membranes, and five on fetal and maternal variables at parturition. Each chapter is followed by a discussion. Unfortunately, there are no chapters on the cervix, a serious omission in view of the importance of cervical factors in labour. The emphasis of the book is on the scientific aspects of the endocrine and paracrine control of parturition and it provides a good update of present knowledge in this important field. However, there is little reference to the clinical and epidemiological aspects of preterm labour. Of necessity, most of the information comes from animal experiments (sheep, small rodents and subhuman primates) and in-vitro experiments on human tissues, but contributions from clinical investigators would have been welcome. The book ends with a useful series of recommendations on the most neglected research areas and the approaches most likely to be fruitful.

The chapters provide a detailed review of the authors' published work and range in style from the factual and descriptive to the hypothetical and speculative. This type of book, where a transcript of a discussion following a live presentation with slides is added to a manuscript submitted separately, has the disadvantage that the reader alone cannot judge the interpretation of the data. Some chapters have no tables or diagrams at all and yet several points in the subsequent discussion are raised by data presented in diagrams that the reader cannot see. The need to do more research on *human* parturition comes through very clearly. There is a consensus that animal experiments are very important in their own right, but have contributed little to our understanding of human labour. It is felt that the mechanisms of action of well-known agents such as oxytocin and prostaglandins need to be elucidated using recent cell biology techniques. A better knowledge of myometrial receptors and cell membrane signalling pathways is required. Several authors emphasize that the search for new endogenous compounds that influence myometrial contractility and cervical ripening must continue, although the feeling is that, as with the role of fetal cortisol in parturition in the sheep, the breakthrough in our understanding of human parturition will be the discovery of a new function for a well-established hormone or agonist.

The book is well presented, but with five editors it is somewhat disappointing that spelling mistakes and other errors have found their way into the final text. Cross-reference is difficult because the chapters are not numbered; also in the text the references are sometimes cited by numbers and sometimes by authors and year. Overall, this is a very important publication for those interested in parturition and a good source of research ideas for workers in this field. It provides an update on the work of several American and Antipodean centres and I think it serves well the purpose of stimulating basic research on a major obstetric problem.

Andrés López Bernal

Pelvic Surgery: A Multidisciplinary Approach edited by John H. Isaacs & Mitchell P. Byrne. Futura Publishing Company, New York, 229 pages with figures and tables, $32.50

This is yet another multi-disciplinary transatlantic tome in which the reader is led through a succession of chapters describing extremely complicated aspects of pelvic surgery. Most such operations could only be carried out in large teaching institutes where several different surgical experts can be gathered together for any one operating list. Polysurgery is beyond the facilities of most of us working in district general hospitals. It is a bible for super-specialists and sub-specialists which of course follows on from the current popularity of such appointments. Much of the book discusses extreme rarities such as retroperitoneal tumours and 'metastatic diseases presenting as a pelvic mass'. There are interesting chapters on vascular 'considerations' when working in the pelvis.

This book could be usefully read by a post-MRCOG student or someone intending to specialize in advanced pelvic surgery. It is well written and edited and at £18.50 is easily affordable by most hospital libraries.

John M. McGarry

Female Genital Cancer edited by S. B. Gusberg, Hugh M. Shingleton & Gunter Deppe. Churchill Livingstone, Edinburgh, New York, 1988, 857 pages with figures and tables, £95.00

It is obvious that the volume of medical information published in the journals far exceeds the ability of the individual to assimilate it. This has resulted in the development of various specialties within medicine, and more recently as the body of knowledge has continued to expand, the development of subspecialties. Gynaecological oncology is such a subspecialty. There will be those who can rightly consider themselves to be subspecialists and whose knowledge must be much more profound than those who have fewer dealings with gynaecological cancer. The former may of course impart their knowledge to the latter. This they have succeeded in doing in the new textbook *Female Genital Cancer* edited by Gusberg, Shingleton and Deppe. These authors claim that *Female Genital Cancer* is comprehensive but not encyclopaedic. The book is divided into four main sections dealing with basic oncological sciences, clinical science of the disease sites, surgical treatment of genital cancer, and special problems, respectively. This book is therefore a useful reference for doctors preparing for both parts of the MRCOG. In addition, it is a useful source of recent references in gynaecological oncology. Futhermore it offers expert guidance in dealing with a whole variety of problems encountered in clinical practice. Medical students will also find the text valuable where it deals with broad topics such as pre- and post-operative care in pelvic surgery and cancer pain. Other topics which are encountered less frequently in the literature, including psychosocial issues in the care of gynaecological cancer patients, are also addressed in this book.

The authors are all based in the USA and the text therefore refers to clinical practice in that country. Differences will exist therefore around the world, but in no way does this detract from this well-referenced and well-illustrated comprehensive and contemporary textbook.

Ian D. Duncan

Gynecological Decision Making Second edition edited by E. A. Friedman, M. Borten & D. S. Chapin. B. C. Deller, Inc., Toronto, Philadelphia, 1988, 356 pages with figures and tables, £39.50

This multi-author book is written by the staff of Boston's Beth Israel Hospital. Its format is rather unusual: chosen subjects are treated identically by a full-page decision-making algorithm and, on the adjacent page, short notes and a brief up-to-date bibliography.

The book covers the whole practice of gynaecology and includes subjects as varied as routine gynaecological examination, symptoms, disorders, diagnostic procedures, operations and their complications and medico-legal issues. The style allows a huge amount of precise and helpful information in a reasonable size volume. Indeed, it covers some smaller and peripheral subjects better than many current texts. It is aimed at a readership from 'practicing gynecologists to medical students'. This ambition is, I believe, unrealistic. The majority of the text is at MRCOG level.

There are excellent and up-to-date sections on AIDS, laparascopic and hysteroscopic surgery and subfertility investigation and treatment. Perhaps the authors' interests determine the space devoted to some subjects rather than their relative prevalence.

This book addresses fine details of American gynaecological practice, much of which would not be followed in the UK. The sections on medico-legal problems and legal aspects of induced abortion are not appropriate for UK readers.

Professor Friedman's team has produced a wide-ranging, up-to-date and interesting text. I cannot, however, see an obvious place for it in this country because of transatlantic differences in legal and medical practice.

Robert Anderson

Obstetrical Measurements in Ultrasound: A Reference Manual by Alfred B. Kurtz & Barry B. Goldberg. Year Book Medical Publishers, Inc., Baltimore, London, Boca Raton, 1988, 214 pages with figures and tables, £34.00

Professors Kurtz and Goldberg have here compiled, in meticulous and scholarly fashion, a volume which records the many fetal and uterine measurements made possible by ultrasound. They describe in detail standard measurements, such as the biparietal diameter and abdominal circumference, more recently described measurements, such as those of the cerebellum and cisterna magna, and also the frankly obscure. References are comprehensive and recommendations are objective. Tables of important measurement values are included. The subject matter may be a little dry and not appeal to the casual reader, but this is a very useful reference book which should certainly be found in all obstetric ultrasound departments.

If a criticism is to be made it is that the authors give the impression in places of not seeing the wood for the trees. There would be benefit in their considering the larger issues in greater and more critical detail, and deriving general principles from the huge mass of data that they have analysed. What is the best standard of gestational age against which to judge ultrasonography? What is fetal growth retardation and how is it best defined? Should we really continue to accept the traditional sigmoid-shaped birthweight-for-gestational-age curve, or reject it as an artefact?

The authors may or may not wish to consider these points in future editions. There should certainly be future editions to allow the authors to continue to sift through and summarize the constantly expanding literature on the use of ultrasound to assess fetal size and growth.

J. Neilson

Books received some of which may be reviewed at a later date

Birthrights. Law and Ethics at the Beginnings of Life edited by Robert Lee & Derek Morgan. Routledge, London, 1989, 222 pages, £30.00

Controversies in Diabetes and Pregnancy (Volume 2 in the series Endocrinology and Metabolism: Progress in Research and Clinical Practice) edited by L. Jovanovic. Springer-Verlag, Heidelberg, 1988, 260 pages with figures and tables, DM 128.00

Ectopic Pregnancy: Pathophysiology and Clinical Management edited by C. M. Fredericks, J. D. Paulson & G. Holtz. Hemisphere Publishing Company, New York, 1989, 231 pages with figures and tables, £43.00

Diabetes Complicating Pregnancy. The Joslin Clinic Method edited by John W. Hare. Alan R. Liss, Inc., New York, 1989, 206 pages with figures and tables, $49.50

Reproductive Endocrine Therapeutics edited by Robert L. Barbieri & Isaac Schiff. Alan R. Liss, Inc., New York, 1988, 404 pages with figures and tables, $59.50

Endovaginal Ultrasound by Steven R. Goldstein. Alan R. Liss, Inc., New York, 1988, 194 pages with figures and tables, $55.00

Achievements in Gynecology (Volume 17 in the series Contributions to Gynecology and Obstetrics) edited by S. Mancuso. Karger, Basel, 1989, 130 pages with figures and tables, US$65.50, £44.60

Reviews in Perinatal Medicine. Volume 6 edited by E. M. Scarpelli & E. V. Cosmi. Alan R. Liss, Inc., New York, 1989, 239 pages with figures and tables, $96.00

Baillière's Clinical Obstetrics and Gynaecology. International Practice and Research. Operative Treatment of Cervical Cancer Volume 2 Number 4 December 1988 edited by E. Burghardt & J. M. Monaghan. Baillière Tindall, London, Philadelphia, 1988, 735–1057 pages with figures and tables, subscription £35.00, single issue £15.00

Diagnostic and Operative Hysteroscopy. A Text and Atlas by M. S. Baggish, J. Barbot & R. F. Valle. Year Book Medical Publishers, Inc., Chicago, London, 1989, 245 pages fully illustrated, £75.00

Human Embryos: The Debate on Assisted Reproduction by C. R. Austin. Oxford Paperbacks, Oxford University Press, 1989, 163 pages, £6.95

Introduction to Psychosexual Medicine by Ruth Skrine. Montana Press, Carlisle, 1989, 211 pages, £10.95

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COMMENTARY

How the management of erythroblastosis fetalis has changed

The incidence of severe haemolytic disease of the fetus and newborn due to blood group alloimmunization has fallen dramatically following the introduction of anti-D immunoglobulin prophylaxis in the 1970s. Although theoretically haemolytic disease can occur in any fetus which carries paternally derived blood group antigens which the mother lacks, the most potent cause of severe disease remains the one associated with Rh anti-D antibodies developing in an Rh (D)-negative mother with an Rh (D)-positive fetus.

The perinatal death rate in the 1950s due to Rh D haemolytic disease was around 1·5 per 1000 births, equivalent to well over 1000 deaths a year (Urbaniak 1985). Maternal sensitization fell by 70% between 1970 and 1976 and perinatal deaths had fallen to 34 per annum by 1983—a reduction of 96% (Tovey 1986) but maternal sensitization has not and will not disappear completely (Clarke *et al.* 1987). In addition, the proportion of erythroblastosis fetalis (EF) due to other blood group antibodies has risen. Occasionally these antibodies, like anti-D, are the cause of severe fetal anaemia leading to hydrops.

In recent years the number of obstetricians with sufficient experience to be confident in the management of the problem has diminished. *Pari passu,* there have been great technical advances which have led to more effective management. Of central importance has been access to the fetal circulation which has influenced both assessment and therapy.

Diagnostic advances

Fetal blood sampling (FBS) has placed diagnosis and prognosis on a firmer basis. The fetal blood group can be determined and this is particularly valuable if the father is heterozygous. Measurement of the fetal haematocrit or haemoglobin is the most direct assessment of severity. It is also a valuable tool for verifying the accuracy of other, less invasive, methods, a number of which have been studied. Sonographic measurement of placental thickness, extra- and intra-hepatic umbilical vein diameters, abdominal circumference, head/abdominal circumference ratio and intraperitoneal volume have been shown to be unreliable in the absence of ascites (Nicolaides *et al.* 1988*a*). However, sonographic evidence of ascites in fetuses of 18–24 weeks gestation signifies severe anaemia (haematocrit <15%; haemoglobin <4 g/dl) (Nicolaides *et al.* 1985; Chitkara *et al.* 1988), although the threshold for ascites rises with advancing gestation (Nicolaides *et al.* 1988*b*).

Doppler ultrasound presents another non-invasive opportunity for assessment of fetal anaemia. High umbilical vein blood flow (Kirkinen & Jouppila 1983) and blood velocities in the descending fetal aorta (Rightmire *et al.* 1986) have been reported in fetal anaemia, although left and right ventricular outputs were in the normal range in one hydropic fetus (Barss *et al.* 1987). More reliable and consistent results may be obtained as Doppler technology becomes more sophisticated, but at present it does not provide sufficient precision for timing transfusions (Copel *et al.* 1988).

The time-honoured means of determining severity of fetal disease has been the spectrophotometric measurement of the deviation in optical density at 450 nm (Δ OD 450) due to bilirubin in amniotic fluid, an indirect index of fetal red cell destruction (Liley 1961). While this is reasonably reliable in the third trimester, it is less so in the second trimester and can be misleading between 18 and 25 weeks. This is partly because of the practice in some centres of extrapolating Liley's zones backwards in gestation. Nicolaides *et al.* (1986*a*) showed that in 31 severely anaemic fetuses at 18–25 weeks (all had haemoglobin <6 g/dl and 14 were hydropic), only 10 had a Δ OD 450 in the extrapolated upper zone, a 68% false-negative rate. Many fetuses might have died due to failure to intervene and transfuse. This has particular significance for EF associated with anti-Kell antibodies (see below). Conversely, false-positive results may lead to unnecessary invasive procedures. McKenzie *et al.* (1988) came to similar conclusions, having found that 21% of their Δ OD 453 measurements between 17 and 36 weeks gave misleading predictions of the fetal haematocrit. Should Liley's charts therefore be abandoned in favour of FBS, as advocated by McKenzie *et al.* (1988)? A disadvantage of amniotic fluid analysis is that a single estimation is usually not sufficient, much more reliable information being gained by observing the trend of two or more serial measurements (Whitfield 1970). It is also clear that the Δ OD 450 is very unreliable in the early and mid-second trimester, that the zones cannot be extrapolated back, and that patients at risk of severe early disease should have an FBS. In the third trimester, Δ OD 450 is more reliable although levels may overestimate the severity, that is values in the upper zone may be associated with a surprisingly good fetal haematocrit. Although this could result in some unnecessary transfusions which might have been avoided by FBS, the suggestion by McKenzie *et al.* (1988) is weakened by the 15% perinatal mortality in their 20 pregnancies managed by FBS without transfusion, as well as by their finding that more procedure-related rises in anti-D levels occurred after FBS than after amniocentesis (see below and Bowell *et al.* 1988). It would seem appropriate to retain amniotic fluid analysis in the late second and the third trimesters, using high Δ OD 450 levels as an indication for FBS.

Another diagnostic option that has become available recently is fetal blood grouping in the first trimester, utilizing the fetal erythrocytes that can be washed out of chorionic villus biopsies (CVB) (Kanhai *et al.* 1987). It may be appropriate for women with a severe history and a heterozygous partner. However, a small amount of fetomaternal haemorrhage usually occurs with CVB (Warren *et al.* 1985) which may lead to an increase in antibody level and in the severity of the disease. CVB should therefore be reserved for women with heterozygous partners who would request termination of a D-positive fetus on the grounds that in-utero treatment would probably be unsuccessful. As we shall see below, this is now increasingly unlikely.

Antibodies other than anti-D

Anti-c and anti-Kell are the antibodies most frequently associated with EF, and currently similar principles of management are used to those in Rh (D) haemolytic disease. With anti-c, confusion arises because this is a rhesus antibody developing in a Rh (D)-positive woman. The anaemia in the fetus may be severe enough to cause hydrops *in utero* if appropriate measures are not taken.

However, recent experience with anti-Kell at Queen Charlotte's and at other centres (Mollison *et al.* 1987; Berkowitz *et al.* 1982; Caine & Muller-Heubach 1986) shows that the same criteria cannot be applied. Anecdotal evidence suggests that the antibody causes suppression of effective erythropoiesis in the fetus rather than haemolysis, so that the bilirubin concentration does not rise significantly in the amniotic fluid even in the presence of very severe anaemia. Management of the fetus at risk should be by a combination of early fetal blood sampling for Kell grouping and assessment of anaemia, followed by frequent ultrasound screening if immediate treatment with transfusion is not indicated.

Therapeutic advances

The therapeutic developments in EF are also a result of gaining access to the fetal circulation and enabling intravascular transfusion (IVT). This was first performed fetoscopically into an umbilical artery or vein at the placental cord insertion (Rodeck *et al.* 1981, 1984). The intrahepatic umbilical vein was needled under ultrasound guidance by Bang *et al.* (1982) and this vessel is quite widely used (de Crespigny *et al.* 1985; Nicolini *et al.* 1988*a*). Intracardiac transfusion is performed in some centres (M. E. Hansmann, personal communication) but the fetal mortality may be unacceptably high (Westgren *et al.* 1988). The technique most widely used now is based on the method of ultrasound-guided FBS from the umbilical vein at the placental cord insertion developed by Daffos *et al.* (1984) (Berkowitz *et al.* 1986; Nicolaides *et al.* 1986*b*).

Apart from the use of different sites for IVT there are other variations in techniques. In many centres the fetus is temporarily immobilized by intramuscular or intravenous curare or pancuronium (de Crespigny *et al.* 1985). 'Straight' ('top-up') transfusions are most widely performed although some prefer exchange transfusion (Grannum *et al.* 1986), the rationale being the risk of circulatory overload in a fetus that may already have compromised cardiac function. This fear has been shown to be unfounded, provided at least that straight transfusions elevate the fetal haematocrit into the normal range (40–45%) and not much higher; such transfusions have increased the feto-placental blood volume by as much as 100% and have been given at a rate of 5–15 ml/min without obvious adverse effects (Nicolaides *et al.* 1986*b*), and only minor changes in acid-base and blood gas status (Nicolini *et al.* 1988*b*). Umbilical vein blood pressure has been measured before and after IVT (Nicolini *et al.* 1989) and rises of up to 12 mmHg (mean 4·6 mmHg) are well tolerated. Straight transfusions also have the advantage of being completed in <30 min whereas exchanges may take up to 3 h.

IVT ensures immediate correction of fetal anaemia and is particularly valuable in hydrops, when intraperitoneal transfusion (IPT) is often ineffective due to slow absorption. Reversal of hydrops has now been observed many times following IVT, whereas IPT may in such cases lead to fetal death. Does this mean that IPT can be left on the scrap-heap of discarded procedures? Certainly not, since it is usually easy, it is very effective in the absence of hydrops and it may also be used in combination with IVT to increase the total volume of blood given to the fetus, thus prolonging the interval between transfusions (up to 4 or 5 weeks) and reducing the total number of invasive procedures per pregnancy (Nicolini & Rodeck 1988).

Knowledge of the fetal haemoglobin before and after IVT enables more rational management of the pregnancy. Appropriate amounts of blood are transfused and timing and spacing of transfusions and delivery can be planned with greater confidence. Pregnancies can be extended late into the third trimester, even if the fetus had hydrops as early as 20 weeks, thus diminishing the need for prolonged neonatal intensive care. There is little to be gained, however, by going beyond 36–38 weeks, and a note of caution may be sounded by the finding that umbilical artery blood of fetuses with adult (transfused) haemoglobin is slightly more acidaemic than blood of those with fetal haemoglobin (Soothill *et al.* 1988). The birth of mature babies, whose own erythropoiesis has been suppressed and who have only rhesus-negative donor blood in their circulation, has also reduced the need for neonatal exchange transfusion; commonly, they require none. However, it may take 3 or 4 months before reticulocytes appear and these infants may need several top-up transfusions.

How good are the results and what are the risks of this treatment? Clearly, experience should be concentrated in a few tertiary referral centres, many of which now quote a 90% survival rate even for early, severe hydrops. Fetal losses are about 2% per transfusion and may be due to cord tamponade or other haemodynamic disturbances. Miscarriage may be associated with amnionitis and rupture of membranes or preterm labour may occur. In general, it is remarkable how many procedures the pregnant uterus can tolerate. Fetomaternal haemorrhage and increased antibody production is a common hazard, and has been found in 50–75% of pregnancies, particularly in association with transplacental ultrasound-guided needling (Bowell *et al.* 1988; Nicolini *et al.* 1988*c*). Mild or moderate disease may become severe, the condition of the fetus may deteriorate rapidly, and future pregnancies may be further compromised. Where possible, transplacental passage of the needle should be avoided and puncture of the intrahepatic umbilical vein rather than the placental cord insertion may ensure this (Nicolini *et al.* 1988*c*). Long-term side-effects specific to IVT have not come to light although a formal follow-up study is still required.

Are any other improvements likely in the future? The possibility of modifying fetal red cell destruction by maternal (or fetal) high-dose IgG therapy is intriguing and merits investigation. However, prevention is by far the most important measure and demands continuing vigilance. Routine antenatal administration of anti-D to D-negative women would lead to further significant reduction of alloimmunization.

Although anti-D immunoglobulin prophylaxis has resulted in an increase in the proportion of EF arising from other fetal–maternal blood group incompatibilities such as anti-c and anti-Kell, there is an absolute reduction in severe cases overall and expertise is now concentrated in a very few centres in the UK.

The advances in both fetal and neonatal care have been dramatic but many obstetricians, paediatricians and haematologists are now completing their basic training without ever having seen a pregnancy complicated by severe or potentially severe EF. It is vitally important to refer couples at risk early in pregnancy or even before pregnancy is embarked upon in certain cases, so that appropriate measures can be taken and strategy planned to give optimal chance of a good outcome.

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What threat is human parvovirus B19 to the fetus? A review

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Ever since Sir Norman Gregg, with his observations on congenital cataracts in children whose mothers had had rubella in pregnancy (Gregg 1941), established an infectious origin for a human congenital defect, the search has been on for other virological causes of fetal damage. Rubella, cytomegalovirus, vaccinia and herpes simplex are now well-established causes of intrauterine infection leading to fetal loss, severe neonatal disease, or congenital abnormality, and there is increasing evidence of a role for varicella zoster (Alkalay *et al.* 1987). Recently, reports have also implicated a relatively newly discovered virus, parvovirus B19, as a cause of intrauterine infection. What evidence is there of a role for this virus, and what are the implications for obstetric practice?

Parvoviruses are single-stranded DNA viruses that replicate in proliferating cells (Hauswirth 1984). They are generally host specific, but are disease agents of a wide range of animals, causing panleucopenia in cats, enteritis in dogs, and epidemic illness in domestic swine, geese and mink (Siegl 1984). Some of the animal parvoviruses can also cause damaging intrauterine infection, the developing embryo offering a wide variety of rapidly dividing and differentiating target tissues. In hamsters, pigs and cattle, infection in the first half of pregnancy is associated with intrauterine death. Fetuses infected later in pregnancy generally survive without clinical disease, but late transplacental parvovirus infection is associated with the development of cerebellar hypoplasia in cats, and myocarditis in dogs and geese (Siegl 1984).

Parvovirus-like particles had been described in human faeces in a number of electron microscope studies (see Paver & Clarke 1976), but it was not until Cossart *et al.* (1975) discovered parvovirus B19 in blood donors' sera, that the existence of a human parvovirus was definitely established. The first disease associated with B19 was transient aplastic crisis, described in six Jamaican patients with sickle cell disease who were attending a London hospital (Pattison *et al.* 1981). Subsequently it was shown that parvovirus B19 can induce aplastic crisis in patients with a wide variety of haemolytic conditions, including sickle cell disease, hereditary spherocytosis, and thalassaemia.

The major manifestation of parvovirus B19 infection in normal people is, however, erythema infectiosum (otherwise known as fifth disease, slapped cheek disease, or academy rash) (Anderson *et al.* 1983). This is a ubiquitous exanthematous disease, mainly of schoolchildren, occurring in localized outbreaks and epidemics in the winter and spring months. The rash most often appears on the face, where the bright erythema gives the 'slapped cheek' appearance, but a lacey reticular rash may be present on the legs, buttocks, neck and trunk. Most children with fifth disease feel well, although there may be a coryzal prodrome, low-grade fever, and/or gastrointestinal upset. In B19 infection of adults, and especially women, polyarthralgia is the dominant symptom with acute symmetrical, peripheral joint involvement lasting days or weeks. Infections may be asymptomatic, both in children and adults.

Diagnosis of parvovirus B19 disease is primarily by serological methods, and radioimmunoassay and enzyme-linked immunosorbent assay are available for the detection of specific IgM and IgG. Early in infection there is an intense viraemia, and parvovirus B19 antigen

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and B19 DNA (detected by nucleic acid hybridization) are present then. These tests are of value in diagnosing aplastic crises in patients with haemolytic disease, all of whom are viraemic in the early stage of crisis, and in-situ DNA hybridization may also be used to look for the sites of B19 replication in other cases of active infection, including suspected instances of materno-fetal transmission (Clewley *et al.* 1987). However, erythema infectiosum viraemia, B19 antigen and B19 DNA are only present in the prodrome of the illness (Young 1988).

Even before the aetiological agent of erythema infectiosum had been identified, its clinical similarity to rubella led investigators to look for evidence of congenital infection. Between December 1961 and June 1962 an outbreak of over 600 clinically suspected cases in Washington State, USA, was described by Ager *et al.* (1966). However, there was no increase in the number of congenital malformations reported locally in 1962 or 1963 compared with earlier or later years, and the authors concluded that there was no evidence of teratogenicity associated with the infection causing erythema infectiosum. Similarly, a study of an outbreak in a small North Devon town (population 3600) during which 32 women were in the first trimester of pregnancy showed no evidence of an increase in miscarriage (n=3) or congenital abnormalities (n=0) compared to the same time period a year earlier (Cramp & Armstrong 1977).

Following the identification of the aetiological agent of erythema infectiosum as parvovirus B19, there were two reports in 1984 describing fetal loss after maternal B19 parvovirus infection in pregnancy. In one of the cases a 'flu'-like illness at 39 weeks was followed 1 week later by a spontaneous stillbirth. The infant was macerated with signs of peritonitis at necropsy. Both maternal and fetal blood had B19 specific IgM, but no viral DNA was detected (Knott *et al.* 1984). The second case was part of an outbreak of erythema infectiosum in North East Scotland (Brown *et al.* 1984). The pregnant woman remained asymptomatic, but routine screening of alpha-fetoprotein at 17 weeks was abnormal and ultrasound scan demonstrated a hydropic fetus. Testing of stored maternal sera showed no evidence of ABO incompatibility, or infection with rubella, CMV or herpes simplex. However, B19 specific IgG and IgM were present with seroconversion occurring between 6 and 15 weeks gestation. B19 viral DNA was detected in the placenta, liver and other fetal tissues. Subsequently a further case of a hydropic fetus associated with maternal B19 infection in pregnancy was reported from the same outbreak (Anand *et al.* 1987).

There have now (March 1989) been seven cases published from the UK where maternal B19 infection has led to a hydrops fetalis, and the clinical features have been remarkably similar (Anand *et al.* 1987; Bond *et al.* 1986; Carrington *et al.* 1987; Anderson *et al.* 1988). Maternal infection between weeks 7 and 16, either clinically expressed (n=3) or asymptomatic (n=4), was followed by the development of hydrops. In those cases where pathological studies were undertaken, the fetuses showed evidence of a leucoerythroblastic reaction and large pale cells with intranuclear inclusion bodies and the presence of B19 viral DNA. In electron microscope studies, particles with the appearance of B19 parvovirus were observed in three of these fetuses (Clewley *et al.* 1987). There are, however, at least 130 cases reported of favourable outcome after confirmed parvovirus B19 infection in pregnancy (Kinney *et al.* 1988).

There is as yet no accurate computation of the risk from B19 to the fetus. In the Scottish outbreak referred to above, six women had serological evidence of B19 infection in pregnancy, of whom four gave birth to normal infants, and two miscarried in the second trimester (Anand *et al.* 1987). A study of 222 pregnant women with non-rubella rashes confirmed B19 infection in eight women in early pregnancy (range 4–17 weeks) (Mortimer *et al.* 1985). Three of these women miscarried (histological studies not reported). Following an outbreak of erythema infectiosum in Mississippi in 1984, four pregnant women with B19 IgM were identified. Three had normal births, but one had a stillborn hydropic fetus (maternal infection at 20 weeks) (Woernle *et al.* 1987). In a study in West Germany of 42 pregnant women, all B19 IgM positive, hydrops fetalis developed in 10 of the pregnancies (Schwarz *et al.* 1988). Taking all these studies together there was hydrops fetalis or fetal loss in 16/60 (26%) of the pregnancies, mostly arising when B19 infection occurred during the first half of pregnancy.

Non-immune hydrops fetalis is rare. It occurs in approximately 1 in 3000 births, and in up to 50% of cases the aetiology is unknown (Warsof *et al.* 1986). In a study in Oxford, 50 patients were examined between 1974 and 1983. In most of them the cause was attributed to cardiovascular anomalies or chomosomal abnormalities, but in 13 the cause remained unknown. However, subsequent examination for evidence of B19 by in-situ hybridization revealed B19 DNA in lung tissue of four of the 13 fetuses, despite there being no known epidemic of parvovirus B19 infection during the study period (Porter *et al.* 1988).

In none of these studies has there been evidence of any congenital abnormality associated with B19 infection, and negative B19 studies on sera from abnormal infants bear this out. Indeed, there is only one recorded case of congenital malformation associated with B19 infection (Weiland *et al.* 1987) In this, maternal B19 infection was confirmed at 6 weeks and the pregnancy was electively terminated for other reasons 6 weeks later. Ocular abnormalities similar to those seen in rubella were observed, but B19 DNA was detected in placenta and fetal tissue and there was no evidence of rubella infection. It can not be known whether this fetus would have been viable if the pregnancy had been allowed to continue.

The pathogenesis of parvovirus B19-associated fetal damage appears to be similar to that leading to aplastic crisis in haemolytic disease. B19 virus is known to infect erythroid progenitor cells and inhibit their replication, and this combined with the shortened red cell lifespan in the fetus leads to erythroblastic hypoplasia (Gray *et al.* 1987). During the second trimester there is a massive increase in the red cell mass and this could explain why the fetus appears to be at greatest risk of hydrops then. By the third trimester the fetus is more able to mount an immune response to the virus, which may account for the decreased rate of fetal loss at this stage of pregnancy.

The Public Health Laboratory Service Working Party on fifth disease has just completed the first part of a study of B19 in pregnancy. In this study 190 women with confirmed B19 infection during different stages of pregnancy have been recruited, and the incidence of fetal infection, fetal loss and long-term sequelae are being followed. It is hoped that this will clarify the risks to the fetus, and improve management of those women who may have been infected The preliminary analysis of the study shows that there was a slightly increased risk of fetal loss following B19 infection, especially in the second trimester when it was 13%. Nevertheless, 83% of B19 infected women gave birth to a normal live infant (S. Hall, personal communication).

Bearing in mind the limited availability of diagnostic tests for B19 infection and the as yet unproven nature of intrauterine treatment of hydrops due to fetal B19 infection, what should an obstetrician do if he suspects B19 infection in a woman under his care? No satisfactory answer can be given to this question at present, but the following points are relevant in assessing suspected cases:

1. B19 infection occurs mostly in association with outbreaks of erythema infectiosum in the late winter and spring. Only 23–45% of pregnant women are susceptible to B19 (Mortimer *et al.* 1985).
2. Quarantine is not recommended for erythema infectiosum as patients are mainly infectious during the viraemia, which occurs a week before symptoms appear. In contrast, patients with aplastic crises or chronic haemolytic anaemia due to B19 infection should be regarded as infectious.
3. As parvovirus B19 has not been shown to cause congenital defects, therapeutic abortion is not indicated for B19 infection.
4. At least 80% of pregnancies in which B19 infections occur result in normal livebirths.
5. Serological tests for B19 infection are only available at a few laboratories, but pregnant women with typical features of B19 infection (erythema infectiosum, acute symmetrical arthralgia) or a history of a contact with a known case of B19 infection, should be investigated where possible. In cases of suspected intrauterine infection and unexplained cases of non-immune hydrops fetalis, tests may be available that can be applied to cord blood, fetal tissues and/or placenta.
6. In cases of proven B19 infection the monitoring of maternal serum for raised alpha-fetoprotein levels and serial ultrasonography have been recommended for assessing the risk of developing hydrops (Carrington *et al.* 1987). In a very limited number of cases intrauterine exchange transfusion has been performed with a satisfactory outcome. These infants are now being followed up (Schwarz *et al.* 1988; PHLS Working Party, unpublished results).

The threat of parvovirus B19 infection to the fetus is still being assessed. Further studies are needed to assess the risk at different stages in pregnancy and to establish what proportion of stillbirths and fetal hydrops are due to B19. Only when a renewable source of antigen has been devised will serological testing become freely available, and more research is therefore needed to develop an adequate expression system for B19 proteins. Once this is achieved, vaccine development will also be feasible. In the meantime the value of maternal alpha-fetoprotein measurement and ultrasound as prognostic indicators, the long-term benefits and complications of intrauterine transfusion, and the possible use of immune globulin as prophylaxis for exposed women need to be investigated.

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Fetal pathology in human parvovirus B19 infection

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Summary. In a current Netherlands study on the effects on mother and child of infection with the human parvovirus B19 during pregnancy, 10 pregnancies have been reported. Three of them ended before term: two in fetal death and one by elective abortion. In two of these fetuses B19 infection in cells other than those of the erythroid series was demonstrated, and in the one terminated, ocular malformation and extensive inflammatory reactions in all fetal and placental tissues were found. The presence of B19 DNA was demonstrated by dot hybridization in placental and fetal tissues. In the third no gross fetal abnormalities were found, although B19 DNA was detected in several fetal tissues by in-situ hybridization. Of the remaining seven pregnancies, six ended at term in the birth of apparently healthy babies. The other child was born near term with a low birthweight and multiple congenital malformations, but with no proof of intrauterine B19 infection. It is concluded that B19 infection in pregnancy can interfere with organ development and may lead to intrauterine fetal death.

The human parvovirus B19 (B19 virus) is known to cause erythema infectiosum and is a major cause of aplastic crisis in chronic haemolytic anaemia (Anderson 1987). During the last few years it has become increasingly clear that infection with this virus in pregnancy may lead to fetal hydrops, fetal death and miscarriage (Brown *et al.* 1984; Mortimer *et al.* 1985; Anand *et al.* 1987; Anderson *et al.* 1988; Porter *et al.* 1988).

A 5-year study to determine the effect of infection with B19 virus during pregnancy was begun in 1986. All women attending the Leiden University Hospital for pregnancy check-ups are asked to participate and all participants provide three serum samples during the pregnancy. Where indicated, additional sera or other materials are collected and the participant is asked to fill in a questionnaire. In addition, physicians throughout the Netherlands are urged to report all cases of suspected B19 infection in pregnancy.

We report here nine women with either proven or suspected B19 infection in pregnancy and one with possible B19 infection. Fetal pathology is described in detail in two patients, one of whom (patient 1) has been reported previously by Weiland *et al.* (1987).

Patients and methods

Patients were selected for this study if, after a history of a rash, arthralgia or contact with a

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person with erythema infectiosum, recent B19 infection was serologically proven or strongly suspected. The diagnosis of infection by parvovirus B19 was established by detecting virus-specific IgM or a rise in antibody titre to virus-specific IgG or both. The 10 patients included in the study are detailed in Table 1.

Serological and DNA hybridization studies were used in the detection of intrauterine B19 infection, as described below.

Serological diagnosis

Maternal serum samples were obtained from all patients. Cord blood was taken from four of the seven livebirths, and in another baby a blood sample was obtained from the heel. No neonatal serum was collected from the other two infants. Follow-up sera were collected from six of the seven children. Sera were tested for B19-specific IgM and/or IgG by an antibody capture radioimmunoassay (Cohen *et al.* 1983). The presence of B19-specific IgM in cord blood and/or B19-specific IgG persisting in a child's serum to the end of the first year was considered proof of intrauterine B19 infection.

Recent maternal rubella virus infection was excluded by standard ELISA-IgM techniques (Rubanostika IgM, Organon Teknika).

Fetal and placental tissues

In each of the three pregnancies which terminated in the first and early second trimester all available fetal and placental tissues were collected. In patient 1 both fetal and placental tissues were obtained at curettage. A portion of the placenta was stored at −70°C; the remaining placental tissue, the umbilical cord and several fetal tissues were fixed in formalin. In patient 2 the only tissue available for this study was formalin-fixed placental tissue and some macerated fetal limb tissue. In patient 3 some placental and several fetal tissues were stored as formalin-fixed paraffin blocks and part of the placenta in formalin.

Slides for teratological, pathological and virological studies were made from all formalin-fixed tissues and stained with haematoxylin-eosin (HE) or Azan. Frozen placental tissue was stained with peridoxase-labelled Leu 2 antibodies (Becton Dickinson, USA) to identify cells in lymphocytic infiltrates. Liver tissue was stained with Perl's Prussian Blue to detect ferric iron.

B19-specific DNA was detected by dot hybridization or in-situ hybridization, using a molecularly cloned probe (Anderson *et al.* 1985). Both methods have been described in detail previously (Clewley 1985; Haase 1986; Salimans *et al.* 1989) and are outlined here. DNA was recovered by phenol-chloroform extraction and concentration by subsequent precipitation in ethanol at −70°C, after overnight digestion with proteinase K. The extracted DNA was examined by dot hybridization using a nick-translated [^{32}P]-labelled B19 DNA probe.

In in-situ hybridization both the presence and the localization of B19 DNA in tissue sections was examined with a [^{35}S]-labelled B19 DNA probe. After deparaffinization, proteinase K treatment and hybridization, the tissue sections were exposed for either 2 or 7 days to photographic emulsion and counterstained with HE.

Results

Details of the 10 patients are given in Table 1. Of the 10 pregnancies, two ended in the first trimester and one at the beginning of the second. Six ended at term in normal livebirths and one at 37 weeks with the birth of a small-for-gestational-age infant with several congenital malformations (birthweight 1720 g, crown–heel length 44 cm).

Serology

Recent maternal infection with rubella virus was excluded in all patients. Results of B19-specific antibody testing are listed in Table 1. All patients, except no. 4, had detectable quantities of B19-specific IgM. In six patients (1, 2, 5, 6, 7, 8) decreasing B19 IgM titres were demonstrated in subsequent samples. In five patients (6–10) maternal sera were not tested for B19-specific IgG. In 4 patients (1, 2, 3, 5) maternal B19-specific IgG was present in high titres (Table 1). Patient 4 demonstrated seroconversion for B19-specific IgG between samples obtained 8 months before conception and another taken after 14 weeks gestation. This patient had signs and symptoms suggestive of B19 infection at 4 weeks gestation; B19-specific IgM was not detected.

Cord blood was collected in four infants (6, 7, 8, 10) and a heel-prick blood sample was obtained in one infant (no. 9) at 4 days of age.

Table 1. Clinical and serological data

Patient no	Gestation at first symptoms (weeks)*	Symptoms of infection	Duration of symptoms (days)	Outcome of pregnancy	Serological results†					
					Maternal			Infant		
					Gestation (weeks)	IgM	IgG	Age	IgM	IgG
1	5–6	Pain, stiff joints, rash on one arm, sore throat, slight fever	5	Elective abortion	7	+	++			
					11 (day of abortion)	±	++			
					4 weeks later	±	++			
					3 weeks later	–	++			
2	10	Arthralgia, myalgia, fatigue	5	Fetal death at 11 weeks	4 weeks after fetal death	+	+++			
					5 weeks later	±	++			
3	15*	None, son had erythema infectiosum	—	Fetal death at 20 weeks	1 week after fetal death	+	+++			
4	4	'Flu-like illness, rash on limbs and face, arthritic fingers	30	Healthy baby at term	8 months before conception	–	–	8 months	NT	–
					14	–	+			
5	5*	None, son had erythema infectiosum	—	Healthy baby at term	8	+	++	9 months	NT	–
					11	±	+++			
6	≤6	None, abdominal rash 3 months after infection	—	Healthy baby at 40 weeks	8	+	NT	Cord blood	–	NT
					21	±	NT	9½ months	NT	–
					35	–	NT			
7	8	Arthralgia knees and ankles, rash on arms and legs	7	Healthy baby at 41 weeks	7	++	NT	Cord blood	–	NT
					9	+	NT	8 months	–	–
8	10	Rash, arthralgia	6	SGA baby with multiple malformations at 37 weeks	10	+	NT	Cord blood	–	NT
								6½ months	NT	–
9	11	Arthralgia fingers, rash on limbs, back and buttocks	NK	Healthy baby at 37 weeks	11	+++	NT	4 days	–	NT
					23	NK‡	NT	13 months	–	–
10	14	Fever, headache, diarrhoea, rash, lymphadenopathy	NK	Healthy baby at 42 weeks	16	++	NT	Cord blood	–	+

* Where the patient was without symptoms the time of infection was estimated.

† Serological results are given in arbitrary units (au) as follows. – = 1 au, ± = 1–5 au; + = 5–25 au; ++ = 25–50 au; +++ = >50 au NT, Not tested; NK, not known.

‡ Positive, but number of au not known

None of these samples contained detectable B19-specific IgM.

Permission to take follow-up sera from the child was refused by one patient (no. 10). In the remaining six children follow-up sera were taken between the ages of 6·5 and 13·5 months. None of these sera contained detectable B19-specific IgG.

Case histories

Three pregnancies terminated in the first or second trimester.

Patient 1. A previously healthy 33-year-old mother of three young children experienced severe arthralgia, with stiffness beginning in the wrists and knees and later involving hips and small finger joints at 5 weeks in her fourth pregnancy. On the third day of her illness an erythematous rash was noted on one of her arms. A sore throat and a slight fever were the only other symptoms. The illness lasted approximately 5 days. A serum sample taken on the fourth day contained B19-specific IgM, indicating recent B19 infection. The couple decided to terminate the pregnancy. Suction curettage was performed at 11 weeks gestation (gestational age confirmed by ultrasound).

Patient 2. A 29-year-old mother of two healthy children experienced a 5-day period of arthralgia, myalgia and fatigue at 9 weeks in her third pregnancy. At 15 weeks a missed abortion was diagnosed; fetal death probably occurred at 11 weeks. Both her children had had an illness resembling erythema infectiosum at the time of this patient's symptoms.

Patient 3. A 34-year-old mother of two healthy children had had an unexplained miscarriage at 11 weeks in her third pregnancy, and underwent suction curettage. Ultrasound scanning 17 weeks after curettage showed a new pregnancy with a normal fetus of approximately 15 weeks gestation. Six weeks later fetal movements stopped and fetal death at 20 weeks gestation was confirmed by ultrasound scanning. Labour was induced and a macerated male fetus was born without obvious macroscopic defects. A serum sample obtained at this time was equivocal for B19-specific IgM and positive for B19-specific IgG, consistent with infection 2 to 3 months previously. The mother had not had symptoms suggestive of B19 infection in this pregnancy, but the family doctor had diagnosed erythema infectiosum in her son some 3 weeks before fetal death.

Examination of products of conception

Placental and fetal tissues were subjected to microscopic and hybridization studies. Special staining techniques were used if indicated on initial screening.

Patient 1. The arteries of the umbilical cord showed localized absence of the endothelium and degeneration of the underlying vascular wall. In the heart, generalized myo-, epi- and endocarditis were noted. Skeletal muscle tissue of the foot and thoracic body-wall showed diffuse myositis and reduction of the number of fibres. The ocular muscles also showed diffuse myositis. Both eyes had structural abnormalities; one eye was of normal size but had retinal folds. In some areas the folds were fused. In addition, lens fibres and nuclei were irregularly positioned and showed degenerative changes. The differentiation of the retina and optic nerve was normal for the gestational age. The other eye was microphthalmic and contained no anterior chamber, iris or lens (Fig. 1). The pigmented layer of the retina was folded and locally interrupted, while the nervous layer was fragmented and hypoplastic. The diameter of the optic nerve was smaller than in the normal-sized eye. In the liver, focal necrosis was observed. In the respiratory tract the bronchial epithelium showed patchy degenerative changes. Perivascular mononuclear infiltrates were noted in all tissues examined, but they were most pronounced in placenta, heart muscle, skeletal muscle and respiratory tract. The mononuclear cells in the placenta were identified as belonging to the T-cytotoxic/T-suppressor group by the presence of CD-8 antigen on their cell membrane. Large nuclei with vacuole-like inclusions were found throughout the fetus (Fig.2). These 'vacuoles' sometimes contained a round body of condensed material (Fig.3) Dot hybridization studies of placental tissue and tissues of the fetal thorax gave positive results, but no tissues contained localized B19 DNA in such amounts that it was detectable by in-situ hybridization.

Patient 2. No perivascular infiltrates and no

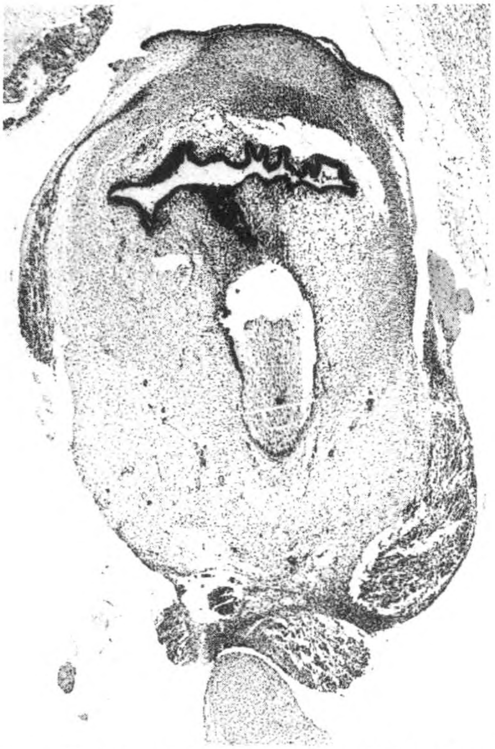

Fig. 1. The microphthalmic eye, with a thickened cornea, absence of the anterior chamber and lens. In the centre the nervus opticus is present.

abnormal nuclei were noticed in the limited fetal material available. In-situ hybridization of these tissues was negative, as was dot hybridization on placental tissue.

Patient 3. Neither the placenta nor the fetus showed macroscopic abnormalities. Microscopical examination of the placenta showed perivascular infiltrates similar to those in patient 1. The fetal thymus was 'empty', as is seen in stress thymus. In some areas of the heart the number of muscle fibres was reduced. The interstitium of the lungs contained patches of mononuclear cells, and there were numerous macrophages in the bronchial lumina, indicating phagocytotic activity. Many macrophages were present in the liver, and haemopoiesis was below the normal level for this gestational age; there was also extensive deposition of a crystalline substance which was shown to contain ferric iron, indicating it to be haemosiderin. Cells with abnormal nuclei similar to those observed in patient 1 were found in all tissues examined, including erythroid cells (Figs 4 & 5). B19 DNA was detected in erythroid and leukoid cells in placental and several fetal tissues by in-situ hybridization.

Discussion

It must be stressed that the present study permits no conclusion on the incidence of B19 infection in pregnancy. Current studies of unselected pregnancies in England, the Netherlands and elsewhere may be expected to provide this information (Hall 1985; Hall *et al.* 1987). In our patients B19 infection in pregnancy was proven or strongly suspected, and in one woman B19 infection was demonstrated by seroconversion in an 11-month period. We have demonstrated transmission to the fetus in two pregnancies which ended in fetal death.

In patient 1 the fetus was alive at the time of curettage, but would certainly have succumbed to the infection. In patient 3 fetal death occurred after a period of fetal stress, as indicated by the finding of 'stress thymus'. In both pregnancies the placenta contained mononuclear perivascular infiltrates. In a portion of frozen placental tissue from patient 1 the infiltrates consisted of

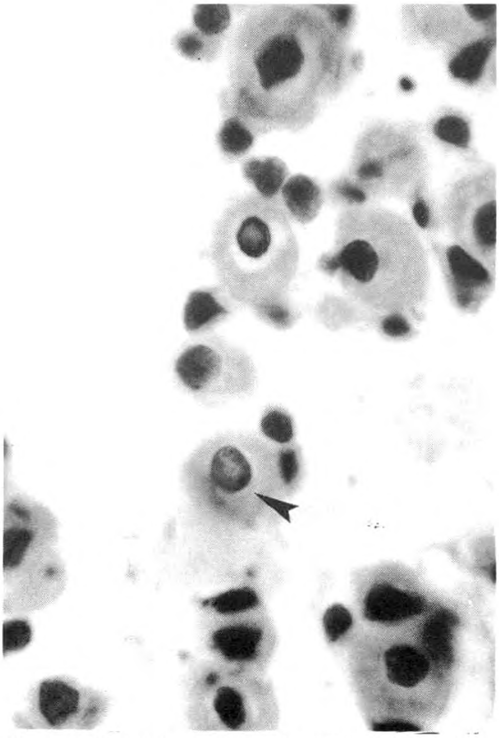

Fig. 2. Inclusion body in muscle cell (arrow-head).

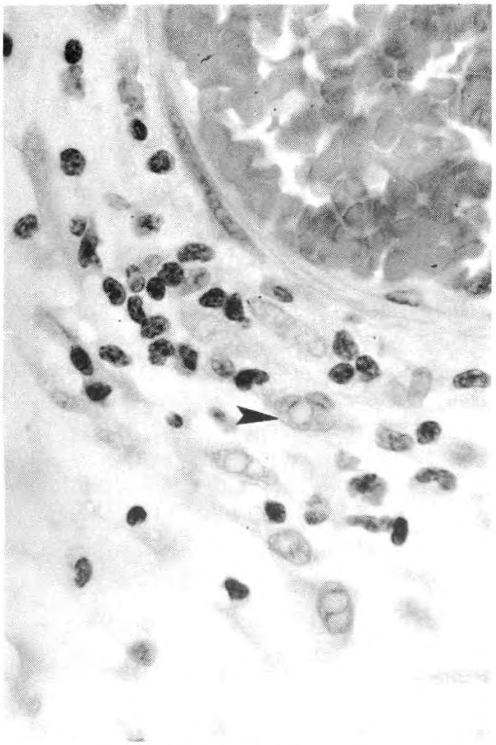

Fig. 3. Inclusion body in placental tissue (arrow-head).

lymphocytes of the T-cytotoxic/T-suppressor group, reflecting a specific reaction. The origin of these T-cells will be discussed elsewhere (Hartwig *et al.* 1989). There is a striking resemblance between the congenital ocular malformations in patient 1 and those reported in rubella (Vermey-Keers 1975) but histologically the abnormalities were clearly more extensive than those found in rubella. Furthermore, the perivascular mononuclear infiltrate noted in patients 1 and 3 has not been described in rubella.

In both these cases cells with large nuclei and intranuclear vacuole-like inclusions were noted in several fetal tissues. Some of the vacuoles contained a round body, the nature of which remains to be determined. These inclusions are compatible with a DNA virus infection. Others have reported similar changes in erythroid and in liver cells, and very recently in various other fetal tissue cells (Anand *et al.* 1987; Anderson *et al.* 1988; Porter *et al.* 1988; Burton 1986). In patient 2, B19 DNA was demonstrated in fetal phagocytic cells. It is likely that these macrophages had phagocytosed cells damaged by B19 infection, thus taking in B19 DNA. Unfortunately we were unable to demonstrate B19 DNA in abnormal cells other than erythroid and phagocytic cells. However, others have recently reported positive in-situ hybridization results on similarly affected fetal myocardial cells in a case of intrauterine B19 infection (Porter *et al.* 1988).

Different tissues were affected by B19 infection. In patient 1, infection occurred very early in pregnancy and resulted in massive damage to all fetal tissues. In patient 3, infection took place at the beginning of the second trimester. Here, the overall inflammatory reaction encountered in the fetus was not nearly as strong as in patient 1. However, in patient 3 there was evidence of massive fetal haemolysis before death as suggested by the abundant haemosiderin in the liver, in addition to extremely poor (extramedullary) haematopoiesis.

These findings can be explained in the following way. Parvoviruses in general infect dividing cells, and the B19 virus has a predilection for erythropoietic tissue in children and adults (Young & Mortimer 1984; Saarinen *et al.* 1986). In a very young fetus such as that in patient 1, cells in all tissues are dividing rapidly and may therefore be infected. With increasing differen-

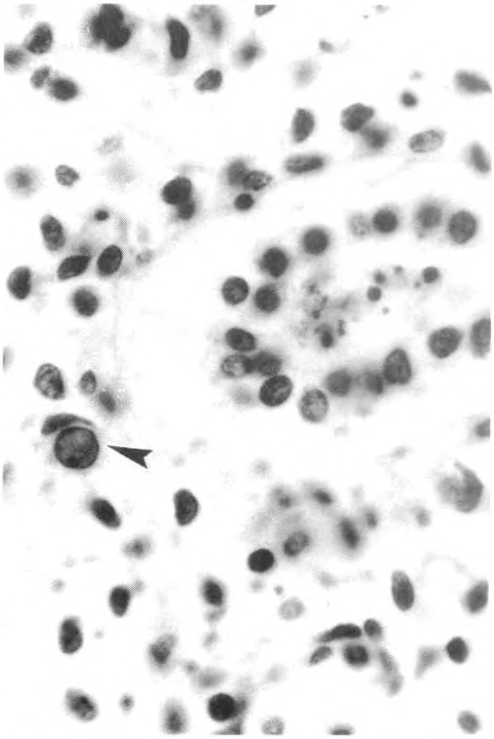

Fig. 4. Inclusion body in erythroid cell (arrow-head).

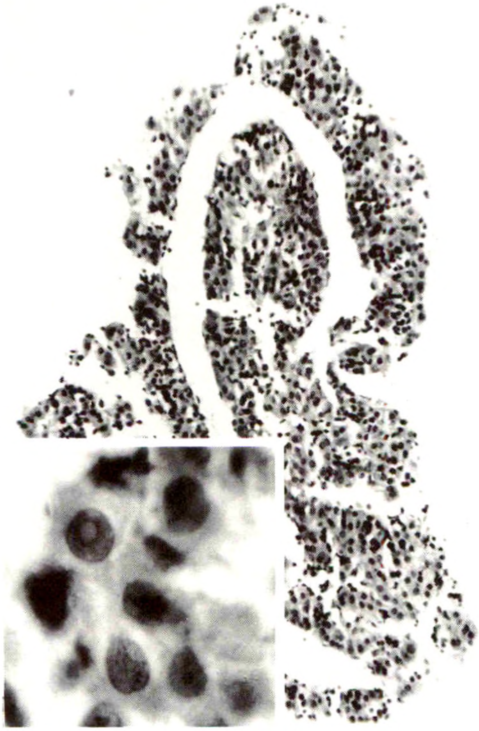

Fig. 5. Inclusion body in liver cell.

tiation of fetal tissues it is possible that the sensitivity for parvoviral infection might diminish in some tissues. Between the third and sixth month of gestation the fetus increases its red-cell mass about 34-fold, and such a fetus has a red-cell lifespan of 45–70 days (Gray *et al.* 1987). Therefore, in an older fetus (no. 3), predominant infection of erythroid cells can be expected. In children and adults, even in B19-induced aplastic crisis in chronic haemolytic anaemia, red-cell lysis is not a prominent feature of B19 infection. The mechanisms operating to produce this lysis in the fetus remain to be determined, although it is possible that differences in expression of viral receptors and the extramedullary site of fetal haemopoiesis may contribute to this marked difference.

Carrington *et al.* (1987) reported a possible correlation between raised maternal serum α-fetoprotein (AFP) and adverse outcome of B19 infection in pregnancy. Raised maternal serum AFP was not detected in any of our three pregnancies with adverse outcome. It is possible that in patient 1, infection occurred too early in pregnancy, before AFP was produced by the fetus, or that the serum samples were collected too soon after the infection, before a rise in AFP production. It has been shown that many factors may contribute to a raised maternal serum AFP level and it is not a very sensitive indicator of fetal pathology (Los 1980). The predictive value of maternal serum AFP for the outcome in fetal parvovirus infection may therefore be limited.

In conclusion, maternal B19 infection is not invariably transmitted to the fetus, as is also shown by others (Mortimer *et al.* 1985; Woernle *et al.* 1987); the factors determining such transmission remain to be elucidated. Pregnancies complicated by maternal B19 infection can result in miscarriage, stillbirth or a healthy livebirth. We conclude that intrauterine B19 infection can interfere with fetal organogenesis and development and may lead to fetal death. Fetal damage may vary with gestational age at the time of fetal infection.

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Are fixed-dose oestrogen/progestogen combinations ideal for all HRT users?

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Summary. Although progestogens protect the endometrium against excessive oestrogen-induced stimulation, they can cause adverse symptomatic and psychological effects and may have undesirable metabolic consequences. Thus, the minimum progestogen dose which results in consistent endometrial transformation should be prescribed. To define this dose for norethisterone and dl-norgestrel, 197 endometrial samples obtained from postmenopausal women receiving conjugated equine oestrogens (0·625 mg or 1·25 mg daily) with one of six doses of norethisterone (or the acetate), or one of three doses of dl-norgestrel added for the first 12 days of each calendar month were examined with the light microscope; 109 samples were also assessed by transmission electron microscopy. There was an inverse relation between the percentage of samples showing proliferative features and the progestogen dose. However, proliferative endometrium was observed in 6% of samples with the highest dose of dl-norgestrel (500 µg) and in 3% of samples with 2·5 mg norethisterone. Conversely, complete secretory transformation was observed in 25% of samples with the lowest dose of norethisterone (0·1 mg) and in 40% of samples with 75 µg dl-norgestrel. Mild atypical hyperplasia was diagnosed in four samples. There was a wide inter-patient variation in response and none of the nine progestogen dose regimens induced secretory change in every patient.

In postmenopausal women, 'natural' exogenous oestrogens have been shown to relieve the short-term symptoms of oestrogen deficiency such as hot flushes, night sweats, and vaginal dryness (Campbell & Whitehead 1977) and have also been shown to prevent longer-term problems such as postmenopausal bone loss (Lindsay *et al.* 1976; Christiansen *et al.* 1980) and to reduce the risk of associated fractures (Paganini-Hill *et al.* 1981; Weiss *et al.* 1980). More recently, it has been reported that oestrogens lower the risk of ischaemic heart disease (Ross *et al.* 1986) and this effect may be mediated, in part, through promotion of a more favourable lipid and lipoprotein profile.

Unfortunately, the administration of exogenous oestrogens is not without hazard. At doses necessary to relieve symptoms and to prevent bone loss, oestrogens stimulate endometrial cell mitosis and proliferation

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(Whitehead *et al.* 1981, 1982*a*) and, when given unopposed, increase the incidence of endometrial hyperplasia (Whitehead *et al.* 1979; Studd & Thom 1981) and carcinoma (Peterson *et al.* 1986). The addition of synthetic progestogens, such as norethisterone (NET) or dl-norgestrel (dl-NG) has been shown to reduce the risk of hyperplasia (Whitehead *et al.* 1979; Studd & Thom 1981) and carcinoma (Gambrell 1986). This protective effect is both dose and duration dependent; 12–13 days of progestogen addition is more effective than 7 or 10 days (Whitehead *et al.* 1982*b*; Studd & Thom 1981). However, NET, or norethisterone acetate (NETA), and dl-NG have potentially adverse effects on lipid and lipoprotein metabolism; they oppose the oestrogen-induced elevation of high-density lipoprotein (HDL)-cholesterol and suppression of low-density lipoprotein (LDL)-cholesterol (Jensen *et al.* 1986; Farish *et al.* 1986). The HDL/LDL-cholesterol ratio is a strong and consistent predictor of arterial disease risk (Gordon *et al.* 1978), a high ratio being more favourable. Thus, by adding one of these progestogens, the beneficial effects of oestrogen on reducing the incidence of arterial disease may be negated.

Reducing the progestogen dose will minimize these potentially adverse effects, but the lower doses may not protect against the development of endometrial abnormalities. Thus, if long-term oestrogen use in postmenopausal women is advocated to reduce osteoporosis and risk of arterial disease, then the progestogen dose should be the minimum at which endometrial safety can be guaranteed.

The current trend in Europe is towards fixed-dose oestrogen/progestogen combinations. Because of the potential side-effects of progestogens, some of the manufacturers have lowered this dose during the past 8–10 years. For example, 'Prempak' (Ayerst Laboratories), containing dl-NG, 500 μg daily for 7 days each cycle, has largely been superseded by 'Prempak-C' containing only 150 μg dl-NG daily but for 12 days each cycle. However, the prescribing of such fixed-dose combinations assumes that there is a single dose of the particular progestogen which is sufficient to provoke endometrial responses in all women.

In a retrospective study of women taking oral oestrogens with either NET, NETA or dl-NG, we sought to determine the minimum dose of progestogen which guarantees consistent endometrial responses.

Subjects and methods

We reviewed all endometrial samples suitable for analysis which were obtained between 1/1/1980 and 31/12/1985. The women were receiving oral conjugated oestrogens (Premarin: Ayerst Laboratories), 0·625 mg or 1·25 mg daily, continuously, and had added one of six doses of NET or NETA, or one of three doses of dl-NG for the first 12 days of each calendar month (Table 1). All patients had been on combined conjugated oestrogen/progestogen therapy for at least 3 months before the endometrial biopsy.

Endometrial samples were obtained by outpatient Vabra aspiration curette (Rocket,

Table 1. Numbers of endometrial samples obtained with each oestrogen/progestogen regimen and source of the progestogen

Progestogen dose	Source	Number of endometrial samples
Norethisterone acetate (mg)		
0·1	Specially supplied by Novo Laboratories	12
Norethisterone (mg)		
0·35	One 'Micronor' tablet (Ortho-Cilag Pharmaceuticals)	49
0·7	Two 'Micronor' tablets (Ortho-Cilag Pharmaceuticals)	25
1·0	Specially supplied by Schering Health Care	4
2·5	Half of one 'Utovlan' tablet (Syntex Pharmaceuticals Ltd)	29
5·0	One 'Utovlan' tablet (Syntex Pharmaceuticals Ltd)	16
dl-Norgestrel (μg)		
75	One 'Neogest' tablet (Schering Health Care)	22
150	Two 'Neogest' tablets (Schering Health Care)	24
500	Specially supplied by Ayerst Laboratories	16

London), but where this proved impossible formal dilatation and curettage were performed under general anaesthesia. All biopsies were taken on the sixth day of progestogen administration. Endometrial tissue for light microscopic assessment was immediately placed into formol acetate: additional tissue (if obtained) was placed into 3% glutaraldehyde in 0·1 M cacodylate buffer for examination using transmission electron microscopy (TEM).

Morphological assessment

Endometrial samples were assessed histologically by conventional light microscopy after haematoxylin and eosin staining. All samples were examined by the same pathologist (J.P.-D.), without prior knowledge of the treatment regimen. The features assessed were those of the normal menstrual cycle and were reported as proliferative, early secretory or late secretory. Additional reported features were non-secretory (absence of mitosis in proliferative endometrium without secretory change) and atypical hyperplasia. The latter was defined as showing both architectural and cellular abnormalities: these were of adenomatous budding, gland crowding, and cellular atypia including nuclear stratification and pleomorphism.

Ultrastructural features were examined and scored by TEM as described previously (Whitehead *et al.* 1981, 1982*a*). The presence of nucleolar channel systems, giant mitochondria, and basal glycogen accumulations (which are features observed between days 17 and 21 of the normal ovulatory cycle (Gordon 1975; Wynn 1977)), each scored one point when present and no score was given when they were absent. The presence of secretory changes on light microscopic examination scored an additional point.

Endometrium for comparison was obtained by dilatation and curettage from premenopausal women who were undergoing laparoscopic sterilization. These samples were taken either during the proliferative phase of the menstrual cycle, or between days 17 and 21 of the secretory phase, and were collected, stored and analysed in an identical manner.

Statistical methods

Statistical analyses of the combined morphological scores were by χ^2-tests

Results

One endometrial sample was obtained from each of 161 patients: 18 women provided one sample during one course of therapy, and a second sample after changing to another treatment regimen. Thus, 197 samples were available for analyses: the numbers of samples obtained with each regimen, and the source of the NET, NETA and dl-NG are shown in Table 1.

Light microscopy

Norethisterone and norethisterone acetate. The numbers of samples (percentages) showing the histological features for the six doses of NET and NETA are shown in Table 2. Two (1·5%) of the 135 samples showed mild atypical changes: one hyperplasia was observed in one (4%) of the 25 samples in the 0·7 mg group, and the second hyperplasia was diagnosed in one (3%) of the 29 biopsy specimens in the 2·5 mg group. Proliferative endometrium was observed in 50% of samples with 0·1 mg NETA, in 8% of samples with 0·35 mg and 0·7 mg, and in 3% with 2·5 mg NET.

dl-Norgestrel. The numbers of samples (percentages) showing the histological features for the three doses of dl-NG are shown in Table 2. Two (3%) of the 62 samples showed mild atypical hyperplasia: both were obtained from the 22 patients (9%) in the 75 μg group. Proliferative endometrium was diagnosed in 27%, 4% and 6% of the biopsies from the 75 μg, 150 μg and 500 μg groups, respectively.

Transmission electron microscopy

Endometrium sufficient for assessment by TEM was obtained from 63 patients receiving NET or NETA (all doses), and from 46 receiving dl-NG (all doses). The data for the three ultrastructural features plus the presence of any secretory activity are presented as number of samples showing the feature/number of samples examined (Table 3). The scores for the premenopausal proliferative-phase and secretory-phase samples were 0 of 44 (0%) and 36 of 36 (100%), respectively.

Norethisterone/norethisterone acetate. The combined scores for 0·1 mg NETA and 0·35 mg NET were 6/16 (38%) and 38/56 (68%), respectively.

Table 2. Number (percentages) of samples showing histological pattern for each conjugated equine oestrogen/progestogen regimen*

Progestogen dose	No. of samples	Histological diagnosis Proliferative *n* (%)	Non-secretory *n* (%)	Early secretory *n* (%)	Late secretory *n* (%)	Atypia *n* (%)
Norethisterone acetate (mg)						
0·1	12	6 (50)	3 (25)	1 (8)	2 (17)	—
Norethisterone (mg)						
0·35	49	4 (8)	16 (32)	24 (50)	5 (10)	—
0·7	25	2 (8)	7 (28)	12 (48)	3 (12)	1 (4)
1·0	4	—	—	2 (50)	2 (50)	—
2·5	29	1 (3)	4 (14)	19 (66)	4 (14)	1 (3)
5·0	16	—	1 (6)	13 (81)	2 (13)	—
dl-Norgestrel (μg)						
75	22	6 (27)	5 (23)	8 (36)	1 (4)	2 (9)
150	24	1 (4)	5 (21)	16 (67)	2 (8)	—
500	16	1 (6)	3 (19)	8 (50)	4 (25)	—

*The regimen comprised oral conjugated oestrogens, 0·625 mg or 1·25 mg daily, and one of the nine stated doses of progestogen for 12 days.

These values were significantly lower than the premenopausal secretory-phase value ($P<0{\cdot}05$). The scores for the higher doses of NET were 43/56 (77%), 12/16 (75%), 57/60 (95%) and 43/48 (90%) for 0·7 mg, 1·0 mg, 2·5 mg and 5·0 mg, respectively, and these were not significantly different from the secretory-phase value.

Table 3. Combined morphological scores for each conjugated equine oestrogen/progestogen regimen*

Progestogen dose	No. of samples	No. of samples showing morphological feature (score) Nucleolar channels	Giant mitochondria	Basal glycogen	Secretory histology	Total score
Norethisterone acetate (mg)						
0·1	4	0	1	3	2	6/16 (38%)**
Norethisterone (mg)						
0·35	14	6	11	13	8	38/56 (68%)**
0·7	14	10	11	13	9	43/56 (77%)
1·0	4	2	2	4	4	12/16 (75%)
2·5	15	15	14	15	13	57/60 (95%)
5·0	12	9	10	12	12	43/48 (90%)
dl-Norgestrel (μg)						
75	15	10	15	14	9	48/60 (80%)
150	17	15	15	16	15	61/68 (90%)
500	14	12	12	13	11	48/56 (86%)
Premenopausal samples						
Proliferative	11	0	0	0	0	0/44 (0%)
Secretory	9	9	9	9	9	36/36 (100%)

*The regimen comprised 0·625 or 1·25 mg conjugated oestrogens and one of the stated doses of progestogen. Premenopausal proliferative- and secretory-phase values are included for comparison.

**Significantly lower than the premenopausal secretory-phase value ($P<0{\cdot}05$; χ^2-test).

dl-Norgestrel. The combined scores for the dl-NG doses were 48/60 (80%), 61/68 (90%) and 48/56 (86%) for the 75 µg, 150 µg and 500 µg doses, respectively. None of these scores differed significantly from the premenopausal secretory-phase value.

Discussion

For reasons stated above, the physician prescribing postmenopausal oestrogen therapy faces a dilemma. Unopposed oestrogens increase the risk of hyperplasia and carcinoma, and the risk of malignant change may persist for as long as 10 years after such therapy is withdrawn (Shapiro *et al.* 1985). Progestogen addition prevents endometrial hyperstimulation but may reduce the benefits conferred by oestrogens in reducing arterial disease risk. A 1% reduction in LDL-cholesterol has been associated with a 2% reduction in arterial disease risk (Lipids Research Clinics Program 1984). Oestradiol, 4 mg daily, reduces LDL-cholesterol by approximately 25% (Jensen *et al.* 1986); the addition of norethisterone, 1 mg daily for 10 days each cycle, halves this reduction. Thus, the lowest progestogen dose needed for endometrial protection must be prescribed.

Progestogens have two distinct mechanisms of action upon the oestrogen-primed endometrium. They suppress the formation of the nuclear oestradiol receptor and also lower DNA synthesis (Whitehead *et al.* 1981, 1982*a*); these actions are considered as the anti-mitotic effect, and suppression of DNA synthesis is represented by 'non-secretory endometrium'. Progestogens also induce the formation of various enzymes (Whitehead *et al.* 1981, 1982*a,b*; Siddle *et al.* 1982), and these actions are represented by 'secretory transformation'. Certain of these enzymes, such as acid phosphatases, are involved in cell autolysis after progestogen withdrawal and, thus, potentially neoplastic cells are shed as a 'withdrawal' bleed. It is not clear which of these two mechanisms is more important in reducing the risk of endometrial hyperstimulation, or whether both are required. Indeed, 'non-secretory endometrium' may precede 'secretory transformation'. Because of these uncertainties, we have classified 'non-secretory endometrium' separately from 'secretory transformation' but we stress that the validity of so doing is questionable.

Proliferative endometrium showing evidence of cell mitosis unquestionably represents inadequate progestational activity. We have attempted to define the lowest dose of norethisterone, or its acetate, and dl-norgestrel which fails to exert reliable and consistent progestational activity upon the endometrium. We think it valid to combine data for 0·625 mg and 1·25 mg/day of conjugated equine oestrogens because these doses achieve similar levels of nuclear oestradiol receptor, an index of oestrogenic stimulation (Whitehead *et al.* 1981, 1982*a*). Our data clearly demonstrate the difficulty of determining this dose for any individual patient. For example, proliferative endometrium was diagnosed in one (3%) patient taking norethisterone, 2·5 mg daily; conversely, six (50%) patients taking norethisterone acetate, 0·1 mg daily, exhibited evidence of progestational activity (Table 2). Increasing the daily dose of dl-norgestrel from 75 µg to 150 µg reduced the frequency of proliferative endometrium from 27% to 4%; however, increasing the dose further, to 500 µg, failed to eliminate this histological pattern entirely, and proliferative endometrium was observed in one (6%) of 16 samples (Table 2). Similar comments apply to the four women with atypical hyperplasia. Norethisterone acetate, 0·7 mg and 2·5 mg, were each associated with one hyperplastic sample, and yet these doses induced secretory transformation in 60 and 80% of samples, respectively (Table 2). Two hyperplasias occurred with 75 µg dl-norgestrel but this lowest dose still achieved secretory transformation in 40% of samples (Table 2). In all four women, the degree of atypia was mild and reverted to normal endometrium after cyclical progestogen therapy (3 weeks on treatment, 1 week off) for 3 months.

The reasons for the wide inter-patient variation in response that we have observed are not known. This may reflect a variation in end-organ sensitivity, or possibly different bio-availability of the oestrogen or the progestogen because of variations in absorption and metabolism. Weight and tobacco consumption may influence bio-availability, but the importance of these factors and the reasons for the inter-patient variation in response can only be determined, in our opinion, from a prospective, controlled trial requiring groups of appropriately matched and selected patients. The current data were derived from a group of unselected women and cannot answer these questions. Therefore, we have made no attempt to determine the effects of body weight and cigarette use upon endometrial histology, and have refrained from presenting these data in this paper. Importantly, however, we believe that our patients are likely to be representative of the patient populations currently treated by most gynaecologists and family doctors in the UK.

Irrespective of the precise mechanisms responsible for the variations in endometrial response, what is important, in clinical practice, is that fixed-dose preparations be designed to maximize the benefit/risk ratio of progestogen addition; and that when these regimens are prescribed the clinician is aware that progestational activity within the endometrium will not be achieved in every patient. Reducing the dose of dl-norgestrel from 150 μg to 75 μg daily was associated with an increase in the percentage of samples showing proliferative endometrium, from 4% to 27% (Table 2); thus, we recommend that 150 μg be considered the minimum dose. The data for norethisterone are more difficult to interpret; 0·1 mg norethisterone acetate is clearly inadequate for routine use (Tables 2 & 3). Increasing the norethisterone dose from 0·7 mg to 2·5 mg was associated with an increase in the combined morphological score (Table 3) from 77% to 95%, and with a reduction in the incidence of proliferative endometrium from 8% to 3% (Table 2). However, caution must be exercised in drawing far-reaching conclusions from relatively small numbers of observations. Regrettably, restrictions on the supply of the 1-mg tablet resulted in few observations in this group. More data are needed on norethisterone doses of 1·0 to 1·5 mg daily: until available, our interpretation of these results is that 0·7 mg is to be preferred to 2·5 mg daily.

How can the small number of patients not responding to these doses of norethisterone and dl-norgestrel be detected? One approach would be to obtain serial endometrial biopsies, but this invasive procedure causes discomfort in an appreciable number of women (Siddle *et al.* 1983) and adds costs. An alternative would be to monitor the day of onset of the withdrawal bleed. We have reported recently that in patients taking continuous oestrogen with 12 days of progestogen added each month, the mean day of onset of bleeding, over 3 consecutive months, correlates reliably with the endometrial histology (Padwick *et al.* 1986). Withdrawal bleeding starting consistently on the 11th day of progestogen addition, or thereafter, was associated with secretory transformation; withdrawal bleeding starting between the 6th and 10th days of progestogen addition was associated with proliferative endometrium. This applied to any oestrogen/progestogen combination except the transdermal system which was not available at the time.

We suggest that in patients taking fixed-dose combination therapies in whom the withdrawal bleeding starts early during the phase of progestogen addition, the progestogen dose be increased. Prempak-C (Ayerst Laboratories) contains conjugated equine oestrogens and dl-norgestrel; the dose of the latter can be increased by adding one Neogest tablet (75 μg dl-norgestrel: Schering Health Care): similarly, the norethisterone acetate component of Trisequens (Novo Laboratories) can be supplemented by the addition of one Micronor tablet (0·35 mg norethisterone: Ortho-Cilag). Clearly, supplementation must coincide with the progestogen phase of treatment in these fixed-dose combinations.

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The effects of oral contraceptives and parity on ovarian cancer trends in women under 55 years of age

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Summary. Mortality from epithelial ovarian cancer is falling in women under 55 years of age in England and Wales. The decline does not appear to be a treatment effect nor to be attributable to changes in the rate of oophorectomy. Case-control studies have shown that high parity and oral contraceptive use are protective against the disease. We suggest that the decrease in mortality is compatible in timing and magnitude with exposure to oral contraceptives. No obvious effect on mortality attributable to parity was apparent in this analysis. Oral contraceptives may prove to be a widely acceptable means of preventing ovarian cancer, providing they do not increase breast cancer risk.

The aetiology of epithelial ovarian cancer is poorly understood, screening is in its infancy, and treatment remains inadequate, as is reflected by the low survival rate (about 25% after 5 years). The investigation of risk factors with a view to primary prevention is therefore important. Case-control studies have provided information on some 25 possible risk factors but only two, parity and combined oral contraceptive use, stand out as playing a major role (Casagrande *et al.* 1979; Cramer *et al.* 1982; Voigt *et al.* 1986; Miller *et al.* 1987; Franks *et al.* 1987; CDC Cancer and Steroid Hormone Study Group 1987).

Parity is the most important known 'natural' factor affecting ovarian cancer risk. Case-control studies have shown a progressively decreased risk with increasing numbers of children although there is some controversy about the possible importance of age at first birth (Cramer *et al.* 1983; Lesher *et al.* 1985; Voigt *et al.* 1986). The protection is of the order of 40% for two children. Beral *et al.* (1978) also demonstrated the protective role of parity in an analysis of vital statistics; a strong negative correlation was found between the age-standardized mortality ratio and average completed family size for women of different generations. However, interest in parity as a risk factor is limited since it offers little scope for prevention.

Quite the reverse is true for oral contraceptives. Every case-control study investigating the effect of the combined pill has found a protective effect against epithelial ovarian cancer. The magnitude of the effect averages about a 50% reduction in risk depending on duration of use (Beral & Franceschi 1985). Combined contraceptives also appear to increase further the level of protection provided by parity by 10 to 30% (Cramer *et al.* 1982; CDC Cancer and Steroid Hormones Study Group 1987). In one study, the protective effect of long-term use (more than 10 years) reached 80%. The benefit was estimated to persist for at least 15 years after discontinuation of the pill and there was a suggestion that exposure for as short a period as 3 months could confer detectable protection with a 5-year latency period before the effect started

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to appear (CDC Cancer and Steroid Hormone Group 1987).

In this paper we consider whether the hypotheses generated by case-control studies on the effects of parity and oral contraceptive use are compatible with ovarian cancer trends in England and Wales.

Subjects and methods

Age-specific mortality and incidence data for each calendar year (between 1950 and 1986 for mortality and 1971 and 1984 for incidence) were obtained from the Registrar General's Statistical Review for England and Wales and the Office of Population Censuses and Surveys publication series. Rates were calculated on the basis of the mid-year female population within each 5-year age group.

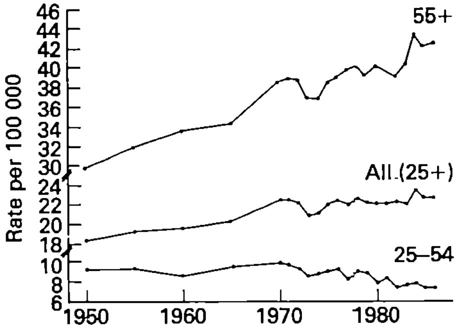

Fig. 1. Age-adjusted mortality rates for ovarian cancer (per 100 000) in England and Wales (1975 taken as standard).

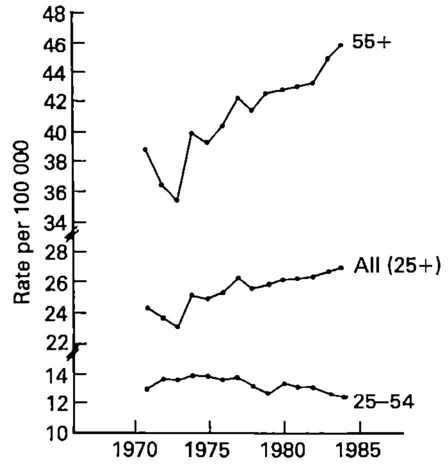

Fig. 2. Age-adjusted incidence rates for ovarian cancer (per 100 000) in England and Wales (1975 taken as standard)

Information on patterns of oral contraceptive use was obtained from three sources: (i) the General Household Survey (OPCS 1983), (ii) Wiseman (1984) who presented data on the total number of pill packets sold each year between 1961 and 1980, and (iii) a group of 1006 women aged 25–54 recruited between 1980 and 1984 as controls in a study of breast cancer risks (McPherson *et al.* 1987). The information from the controls was necessary because no adequate official data are available on the use of oral contraceptives by age group and calendar period.

Data on attained family size were available from OPCS Monitor FM1 86/2 for each birth cohort from 1921 to 1966. This information was complemented by data on age at first birth in the series of controls referred to above.

Results

Ovarian cancer trends

Initial examination of the data showed that the age-adjusted mortality rate from ovarian cancer for all women over 25 increased considerably between 1950 and 1970, but changed little thereafter (Fig. 1). Division of the data into two broad age groups, 25–54 and 55+, revealed an interesting contrast. In the latter age group, mortality increased throughout—29% between 1950 and 1970, and a further 10% up to 1986—while in the former, an inflection point occurred around 1970 with a subsequent decrease in mortality of 26%. Age-specific mortality rates showed that this decrease affected every age group over 30 and that the greatest effect was seen at ages of 40–44 and 45–49 (figure not shown).

Data on incidence, available only since 1971, also showed a sharp rise for the older age group. In younger women, the rate was atypically low in 1971, but between 1972 and 1984 there was a decline of 10% (Fig. 2).

Below age 25, the number of tumours is very small and a considerable proportion are non-epithelial cancers, which have a different aetiology from epithelial cancers. Accordingly, our analyses concentrated on women aged between 25 and 54.

To examine the influence of successive 5-year birth cohorts on cross-sectional trends, the mortality experienced by generations of women born between 1911 and 1955 was tabulated

Table 1. Mortality from ovarian cancer by birth cohort in death rates per million

Age (years)	Birth cohort 1911–15	1916–20	1921–25	1926–30	1931–35	1936–40	1941–45	1946–50	1951–55	1956–60
25–29	13	12	12	9	6	9	8	6	7	6
30–34	21	20	16	20	17	18	14	13	10	
35–39	40	38	39	36	36	31	32	24		
40–44	87	90	84	93	89	74	68			
45–49	164	163	162	175	162	132				
50–54	238	259	247	246	234					

(Table 1). Very little variation was observed among the first three cohorts and since only a negligible proportion of women born between 1911 and 1925 could have been exposed to oral contraceptives, and then only late in reproductive life, these cohorts were taken as a baseline. The mortality of the next two cohorts—1926/1930 and 1931/1935—was essentially the same as that of the baseline cohorts. However, the four subsequent cohorts—1936/1940, 1941/1945, 1946/1950 and 1951/1955—showed a progressively lower mortality at almost every age.

Attained family size

Attained family size by birth cohort increased steadily up to the generation born in 1941–1945 for ages 25 to 34 but was maximum for all ages after 35 for the generation of 1936–1940 (Table 2). From then on a rapid decrease occurred, eventually reaching a level almost as low as the 1921/1925 birth cohort. The data given in Table 2 follow the same pattern as those on age at first birth obtained from the controls in the breast cancer study (figures not shown), suggesting that the control sample is broadly similar to the general population.

Oral contraceptive use

Figure 3 illustrates the dramatic increase in oral contraceptive use after the introduction of the pill in the early 1960s. Consumption peaked at approximately 45 million packets in 1975–1977 and then decreased to approximately 35 million packets by 1980.

The General Household Survey (OPCS 1983) has shown that the proportion of current users has slowly declined from 38% to 28% of the female population of reproductive age since 1973, and the proportion is believed to be under 28% currently. However, the distribution of users within the fertile population has changed dramatically over the years in terms of age and marital status. Figure 4 shows the proportion of women who had ever used the pill, by age, in successive birth cohorts of women, as derived from the control population in the study of McPherson *et al.* (1987). In the 1920–1924 cohort, women started using the pill to prevent further pregnancies after completing their family. In the next three cohorts the pill was also

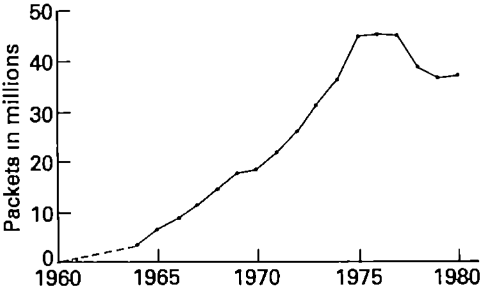

Fig. 3. Oral contraceptive sales in the UK (from Wiseman 1984, published with permission of the author and the editor).

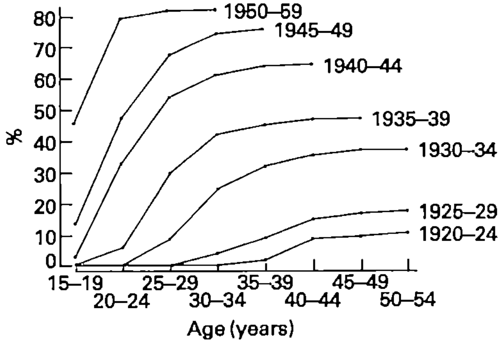

Fig. 4. Cumulative percentages of women with exposure to oral contraceptives by age in successive birth cohorts.

Table 2. Attained family size by age and birth cohort. Mean number of children per woman for England and Wales

	Age (years)					
Birth cohort	20	25	30	35	40	45+
1921–25	0·08	0·58	1·33	1·76	1·98	2·05
1926–30	0·08	0·72	1·41	1·87	2·12	2·18
1931–35	0·11	0·77	1·57	2·10	2·30	2·34
1936–40	0·12	0·90	1·80	2·25	2·38	2·40
1941–45	0·17	1·08	1·89	2·22	2·32	2·34
1946–50	0·22	1·04	1·74	2·05	2·16	
1951–55	0·24	0·89	1·51	1·87		
1956–60	0·20	0·76	1·40			
1961–65	0·16	0·65				
1966–70	0·14					

From OPCS Series FMI(13).

used for birth spacing after marriage. Oral contraceptives subsequently became available to married and single women alike, thereby decreasing age at first use. Finally, access to the pill for everyone, free of charge, was possible following the NHS Amendment of 1972. Thereafter, oral contraceptives rapidly became the preferred method of birth control before first full-term pregnancy. The latest data from a pilot study conducted by the Royal College of General Practitioners (1986) showed that for the 1965/1969 birth cohort, 70% of young women had used the pill before age 20.

Discussion

Since mortality data are more complete, they are discussed here in more detail than incidence data.

The cross-sectional mortality data indicate that since the 1970s the upward trend in the death rate from ovarian cancer has slowed down. This is entirely due to a substantial decline in the death rate of women under 55 years of age (Fig. 1). Death rates from ovarian cancer were fairly stable for successive cohorts of women born between 1911 and 1935. There followed, from 1936, a gradual decline in mortality for each subsequent cohort. The decrease observed in cross-sectional data is therefore mainly due to the lower mortality of women born since 1936. A progressive increase in completed family size in the earlier cohorts—1921/1925 up to 1936/1940—would have led one to expect a decrease in mortality in these groups. This in fact occurred only in the cohort of women born in 1936/1940. Subsequent cohorts showed a sequential decrease in completed family size paralleled by a decrease, not an increase, in mortality from ovarian cancer.

These data do not provide any obvious confirmation of an inverse relation between completed family size and ovarian cancer mortality although it must be stressed that changes in completed family size over the period were fairly small. Thus the variation in completed family size ranged between 2·05 children per woman for the 1921/1925 cohort to 2·4 for the 1936/1940 cohort, a change of 17% (Table 2). The protective effect of parity is not linear according to the findings in case-control studies and can be estimated at under 10% over this range. An effect of this magnitude may be too small to be observable in vital statistics.

Low levels of exposure to oral contraceptives likewise have produced no detectable effect on ovarian cancer mortality trends. Thus, generations of women born between 1920/1924 and 1925/1929 included only 10% and 17% of women, respectively, exposed to oral contraceptives, and they were mostly exposed late in their reproductive life (Fig. 4). This level and pattern of exposure did not appear to be protective in the approximately corresponding birth cohorts, 1921/1925 and 1926/1930, which showed little change in mortality (Table 1). The following cohort, 1930/1934, reached an overall exposure of 34% with little if any effect on death rates. Indeed, an apparent relation only became notable when the next cohort was considered, this group including 50% of women with exposure to the pill with 30% already having such exposure by age 29. Subsequently as the proportion of users increased there was a concurrent decrease in cohort death rates. From all these observations, the evidence seems strong that oral contraceptives are having a favourable effect on ovarian cancer mortality.

A possible bias in the interpretation of cohort trends is the influence of the number of ovaries at risk. Alderson & Donnan (1978) showed that in England and Wales the rate of hysterectomy did not affect perceptibly the denominator in the calculation of cervical cancer trends. Since ovarian cancer is rare in young women and most bilateral oophorectomies occur in conjunction with hysterectomy, it is concluded that the small change in the denominator does not bias the interpretation of results. Furthermore, an approximate assessment of the annual frequency of the operation in the relevant age groups, based on the Oxford Family Planning Association contraceptive study, showed that, of all hysterectomies performed, only 12% were accompanied by bilateral oophorectomy, and therefore confirmed that this factor could safely be ignored. The interpretation of trends, however, remains complicated by factors such as changes in age at first birth. Likewise, the effect of oral contraceptive use is likely to be affected by age at first use and duration of use but probably not by the precise formulation of the preparation (CDC Cancer and Steroid Hormones Study Group 1987). For reasons such as these, vital statistics are insensitive to small changes.

Another bias could occur from any effect that treatment might have on ovarian cancer mortality. Any such effect might be expected to be greater at younger ages. Recent data have shown that 5-year survival rates have changed little between the 1960s and the 1970s although there is an indication that the survival curves at 10 and 15 years are slowly improving (Haybittle & Kingsley-Pillers 1988). The authors are not aware of other possible time-related confounding variables.

The incidence data, although not as persuasive as the mortality data, have also shown a decline in younger women since the beginning of national registration in 1971. The shallower downward trend observed might indicate that the mortality trend is influenced by treatment, as suggested above. It will, however, certainly have been affected by less complete registration in the early years of the scheme. Perhaps the most important fact is that the incidence has not increased in the younger women, whereas it is certainly doing so among women over 55. Unfortunately the incidence data cannot be investigated by cohort analyses since cancer national registration is only 17 years old.

It would appear from the observation of vital statistical data that, first, there is a consistent decrease in ovarian cancer mortality experienced by successive birth cohorts since 1936, and second, that this trend is compatible with patterns of use of oral contraceptives. There is no obvious relation between completed family size and cancer rates in the data. If we assume that the decline in mortality rates is attributable to the pill, then a rough calculation shows that combined oral contraceptives may have prevented about 1500 ovarian cancer deaths between 1973 and 1986 for women aged 25 to 54. In 1986, the last year for which mortality data are available, oral contraceptives may have prevented nearly one-quarter of the deaths from ovarian cancer up to 54 years of age which would otherwise have occurred. Therefore oral contraceptives may prove to be a powerful and widely acceptable means of preventing ovarian cancer, providing they do not increase breast cancer risk.

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Fetal growth achievement and neurodevelopmental disability

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Summary. To investigate the role played by chronic intrauterine insult in the genesis of neurodevelopmental disability (NDD), three analyses have been applied to a case-controlled study which compared a population of children with NDD with a control group of normally developed children. In the first analysis, average birthweight in children with NDD was 3138 g (SD 592) which was significantly less than in normally developed children, 3280 g (SD 491) ($P<0{\cdot}0005$). After correction for confounding factors, birthweight-for-gestation (Z score) remained lower in children with NDD ($-0{\cdot}42$) than normal children ($-0{\cdot}21$) ($P<0{\cdot}0025$). In the second analysis the fetal growth achievement of children, who had NDD after the prenatal complications, severe hypertension, unclassified antepartum haemorrhage and preterm uterine activity, was significantly less (Z score, $-0{\cdot}76$) than children who were normally developed after the same maternal prenatal complications (Z score, $-0{\cdot}37$) ($P<0{\cdot}03$). In the third analysis, a risk analysis to assess the relative importance of fetal growth achievement and prenatal complications in the genesis of NDD suggested that the latter was the dominant factor. These data are consistent with the hypothesis that prenatal complications, severe enough to retard fetal growth, can compromise fetal brain development and make an important contribution to NDD.

In our studies of pregnancy antecedents and child development we found strong associations between prenatal rather than perinatal factors and neurodevelopmental disability (NDD) (Taylor *et al.* 1985). A history of maternal severe hypertension, unclassified antepartum haemorrhage and preterm uterine activity were all more common in disabled children than normally developing children. We also found an increased frequency of small-for-gestational-age infants in the disability group. We have analysed our data further to examine the relations between prenatal complications, intrauterine growth and subsequent disability.

Subjects and methods

In the Dundee Development Screening Programme (Drillien & Drummond 1983) every child born in Dundee in 1974 and 1975 was screened for NDD at 2, 5, 9 and 15 months and 2 and 3 years of age using the development schedules described by Drillien (1977) which are based on those of Gesell (Knobloch & Pasamanick 1974; Knobloch *et al.* 1980). Of the 322 singleton children found to have disability the maternity case records could not be found in 22 cases and we have examined the case records

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of the remaining 300 children for the purposes of this study. The normally developed children born immediately before and immediately after each disabled child, whose case records were available, were selected as control subjects (normal group, $n = 600$). In the disabled group 13 children were found to have specific syndromes and they have been excluded from this analysis, leaving an index group of 287 disabled children (disabled group). Although cerebral palsy may form a separate subgroup (Taylor *et al.* 1985) with different antecedents, their number is small (12) and so they have not been excluded from this analysis in the absence of other evidence supporting our previous data.

Three questions have been addressed:

(1) Are children with NDD lighter at birth than normally developed children?

Comparisons between disabled and normal children were made in respect of birthweight (g), its confounders, maternal age (years), maternal height (cm), maternal weight at 20 weeks gestation (kg), maternal parity (n), infant sex, gestation at birth (completed weeks) and birthweight for gestation (Z score) using a computer programme based on the methods described by Altman & Coles (1980*a*, *b*). The Z score is used here to transform birthweight to a mean of 0 and a standard deviation of 1. Therefore each child's birthweight is converted to a value equivalent to the number of standard deviation units that it is above or below the mean.

(2) Are children with NDD after prenatal complications lighter at birth than normally developed children after the same maternal prenatal complications?

Comparisons of mean birthweight and birthweight for gestation (Z score) were made between disabled children and normal children, stratified by prenatal complications. The prenatal complications were defined as severe maternal hypertension (diastolic blood pressure $>$ 110 mmHg or $>$90 mmHg if there was proteinuria greater than 300 mg/l in a 24-h urine specimen or one plus in a mid-stream urine sample measured with 'Labstix'), unclassified antepartum haemorrhage (vaginal bleeding after 28 weeks gestation of no specific cause and no evidence of maternal hypertension), preterm uterine activity (admission to hospital with painful uterine contractions before 37 weeks gestation, subsequent discharge and readmission for delivery after 37 weeks gestation in the absence of maternal hypertension or antepartum haemorrhage).

In answering questions 1 and 2 the χ^2-test and unpaired Student's t-test were used for the statistical comparison of discrete and continuous variables respectively.

(3) Is fetal growth achievement or the presence of prenatal complications more important in the genesis of NDD?

This question was examined using relative risk analysis.

Results

(1) Are children with NDD lighter at birth than normally developed children?

Mean birthweight in normal children was lower than that in children with NDD (3280 g, SD 491 *vs* 3138 g, SD 592, $t = 3{\cdot}76$, d.f. 885, $P = 0{\cdot}0005$). There were, however, some differences in the confounders of birthweight between the two groups.

Although the maternal weight data are incomplete, 83% being available in the disabled group and 86% in the normal group, the mothers of the disabled children for whom data were available were lighter ($\chi^2 = 10{\cdot}9$, d.f. = 4, $P = 0{\cdot}028$) and more were parous ($\chi^2 = 11{\cdot}5$, d.f. = 5, $P = 0{\cdot}042$) (Table 1). There were, however, no statistically significant differences between the disabled and normal children in respect of maternal age and maternal height. There was an over-representation of male infant sex in the disabled group (disabled = 171, 59·6%, normal = 315, 52·5%, $\chi^2 = 3{\cdot}93$, d.f. = 1, $P = 0{\cdot}047$). The distribution of gestation at birth (Table 2) shows a trend to earlier delivery in the disability group ($\chi^2 = 21{\cdot}98$, d.f. = 4, $P = 0{\cdot}0001$; χ^2 trend = 17·73, d.f. = 1, $P<0{\cdot}00001$), although only 16% of the disabled group were born before 37 completed weeks.

After correcting birthweight for confounders the children with NDD were still significantly smaller, mean Z score = $-0{\cdot}42$, than controls, mean Z score = $-0{\cdot}21$ ($t = 3{\cdot}03$, d.f. = 885, $P<0{\cdot}0025$). The proportion of small-for-gestational-age (SGA) infants ($\geq$1·3 SD below the mean, approximately the 10th centile) was 19·9% in the disability group compared with 11·0% in the normal group ($\chi^2 = 12{\cdot}76$, d.f. = 1, $P = 0{\cdot}0004$).

(2) Are children with NDD after prenatal complications lighter at birth than normal children after the same prenatal complications?

Table 1. The distribution of maternal age, height, weight and parity in disabled and normal groups

Maternal characteristic	Disabled group n (%)	Normal group n (%)	χ^2 χ^2 trend	P
Age (years)				
<19	48 (16·7)	93 (15·5)		
20–24	129 (44·9)	237 (39·5)		
25–29	80 (27·9)	197 (32·8)		
30–34	20 (7·0)	58 (9·7)		
>35	10 (3·5)	15 (2·5)	5·38	0·25
			1·60	0·21
Height (cm)				
<150	42 (14·7)	53 (8·8)		
151–154	45 (15·8)	92 (15·3)		
155–159	95 (33·2)	185 (30·9)		
160–164	69 (24·1)	169 (28·2)		
165–169	30 (10·5)	81 (13·5)		
>170	6 (1·7)	20 (3·3)	10·12	0·07
			8·35	0·004
Weight (kg)*				
<49·9	38 (15·9)	47 (9·1)		
50–59·9	105 (43·9)	219 (42·4)		
60–69·9	64 (26·8)	185 (35·8)		
70–79·9	24 (10·0)	49 (9·5)		
>80·0	8 (3·4)	17 (3·2)	10·19	0·028
			3·97	0·046
Parity (n)				
0	115 (40·0)	290 (48·3)		
1	108 (37·6)	195 (32·5)		
2	42 (14·6)	84 (14·0)		
3	10 (3·6)	23 (3·8)		
4	9 (3·1)	6 (1·0)		
>5	3 (1·1)	2 (0·4)	11·5	0·042
			6·15	0·01

*Incomplete data.

The average birthweight of disabled children whose mothers had not had prenatal complications ($n = 209$) was 3296 g (SD 493) which was not statistically significantly different from the average birthweight of the normal children whose mothers also had no prenatal complications ($n = 546$, mean = 3335 g, SD 445) (t = 0·998, P = 0·32) (Table 3a). In contrast, the average birthweight of the disabled children whose mothers did have prenatal complications ($n = 78$) was less than the average birthweight of the normal children despite having the same complications, 2824 g (SD 677) *vs* 3116 g (SD 570) (t = 2·678, P = 0·0008).

Also, after correction for confounders, birthweight-for-gestation was significantly less in the disabled children exposed to prenatal complications (Z score −0·76, SD 1·05) than those children exposed to similar complications but who were subsequently found to be normally developed (Z score −0·37, SD 1·01) (t = 2·108, P = 0·037).

Table 2. The distribution of gestation in disabled and normal groups

Gestation (weeks)	Disabled group n (%)	Normal group n (%)
<32	4 (1·4)	0 (0·0)
32–34	6 (2·1)	7 (1·2)
35–37	34 (11·8)	37 (6·2)
38–40	181 (63·1)	378 (63·0)
>41	62 (21·6)	178 (29·6)

χ^2 = 21·98, d.f = 4, P = 0·0002.
χ^2 trend = 17·73, d.f. = 1, P = 0·00001.

Table 3. (a) Birthweight and (b) birthweight-for-gestation in disabled and normal children by prenatal complications

(a) Prenatal complications	Disabled *n*	Disabled Birthweight (g) Mean (SD)	Normal *n*	Normal Birthweight (g) Mean (SD)	*P* value
Present	78	2824 (677)	54	3118 (570)	0·008
Absent	209	3296 (493)	546	3335 (445)	0·3187

(b) Prenatal complications	Disabled *n*	Disabled Birthweight for gestation (*Z* score) Mean (SD)	Normal *n*	Normal Birthweight for gestation (*Z* score) Mean (SD)	*P* value
Present	78	−0·76 (1·05)	54	−0·37 (1·01)	0·03
Absent	209	−0·23 (0·99)	546	−0·15 (0·93)	0·39

(3) Is fetal growth achievement or the presence of prenatal complications more important in the genesis of NDD?

The estimated relative risk of NDD was calculated for prenatal complications and birthweight-for-gestation (Table 4). The estimated relative risk for SGA without complications was only 1·4 (95% CI 0·9 to 2·3) but the estimated relative risk increased to 6·6 (95% CI 3·3 to 13·1) if SGA was associated with complications The estimated relative risk for prenatal complications alone was higher than SGA alone at 3·2 (95% CI 2·0 to 5·0).

Discussion

When compared with normally developed children our disabled children were on average lighter at birth and were more likely to be SGA, differences which could not be accounted for by differences in maternal characteristics, infant sex or gestation. The association between disability and SGA at birth is well reported (Taylor 1988). SGA infants are recognized to be at increased risk of cerebral palsy (Alberman 1963; McDonald 1964; Dale & Stanley 1980; Veelken *et al.* 1983) and also impaired development (Drillien 1970; Fitzhardinge & Steven 1972; Neligan *et al.* 1976; Fitzhardinge *et al.* 1978). However, in our study the association of prenatal complications with disability was stronger than retarded growth alone. This relation between prenatal complications and disability held whether infants were small or appropriately grown at birth although the effect of prenatal complications was stronger when the infants were small.

The literature provides some support for a finding of a relation between prenatal complications and subsequent childhood disability. Severe hypertension has been associated with subsequent handicap (Lilienfeld & Pasamanick 1955; Szymonowicz & Yu 1987) and disability (Barker & Edwards 1967; Ounsted *et al.* 1980).

Table 4. The estimated relative risk of neurodevelopmental disability

Pregnancy group	Disabled (*n*)	Normal (*n*)	Estimated relative risk (95% confidence interval)
AGA, no complications	181	492	1·0
SGA, no complications	28	54	1·4 (0·9 to 2·3)
AGA, complications	49	42	3·2 (2·0 to 5·0)
SGA, complications	29	12	6·6 (3·3 to 13·1)

AGA, Appropriate-weight-for-gestation; SGA, small-for-gestation.

Similar relations have been demonstrated for antepartum haemorrhage (Neligan *et al.* 1976; Hagberg *et al.* 1976; Weindling *et al.* 1985; Nelson & Ellenberg 1986).

In our study, within groups of prenatal complications, it appeared that disability was found only if birthweight was significantly reduced whereas development was normal if normal birthweight was attained. This would suggest that the quality of the prenatal environment as reflected in fetal growth achievement is important to the growth and maturation of the fetal brain and subsequent development. Neligan *et al.* (1976), Sabel *et al.* (1976) and Fitzhardinge *et al.* (1978) have reported a relation between poor fetal growth and subsequent impaired development, and Hagberg *et al.* (1976) have stressed the importance of what they termed fetal deprivation of supply in the aetiology of cerebral palsy. Since fetal growth was impaired in our disabled group it would be reasonable to suggest that the mechanism whereby prenatal complications are related to subsequent disability is impaired placental transfer, restricting fetal brain growth and development. Perinatal hypoxaemia/acidosis secondary to impaired placental transfer may also play a role in the genesis of the disability.

An alternative explanation would be that the prenatal complications and poor growth are associated with fetal malformation and so are not the cause of disability. However, fetal malformation does not appear to be associated with severe hypertension (Scott 1958; MacGillivray 1959; Clinch 1980). There is less information about antepartum haemorrhage and fetal malformation. Both Hibbard & Jeffcoate (1966) and Paterson (1979) quote fetal malformation rates of 3·1% in association with placental abruption compared with a rate of 1·3% in the general population. However, placental abruption is related to increasing maternal age, parity and decreasing social class, all of which are associated with increased fetal malformation rates. A controlled study of fetal malformation in antepartum haemorrhage, matching controls for maternal age, parity and social class, or a multivariate analysis is required to examine this relation further.

Two recent leading articles (Editorial 1979; Chiswick 1985) stated that intrauterine growth retardation, other than very severe growth retardation, seems unlikely to pose any substantial threat to neurodevelopmental outcome unless it is associated with, firstly, chromosomal abnormalities or dysmorphic syndromes or, secondly, perinatal complications such as severe asphyxia, symptomatic hypoglycaemia or hyperviscosity syndrome. Our data are not consistent with the view that only very severe growth retardation is likely to pose a threat to neurodevelopmental outcome. Many of the disabled children, although not growth retarded by a definition of birthweight <10th centile, must have failed to achieve their ideal birthweight because the birthweight distribution of the disabled group was shifted downwards. If our observations are confirmed, it would suggest that prenatal events, particularly prenatal complications associated with intrauterine growth retardation, may have greater importance for subsequent disability than those during labour. Intrapartum events are more readily amenable to intervention but it may well be that the antepartum period, although less accessible, carries greater ultimate clinical significance. Understanding of the mechanisms involved in the relation between these prenatal complications and childhood disability has important clinical implications as management strategies of these complications designed to improve the outcome of the children can only be developed and tested in the light of such understanding.

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The role of low-dose methotrexate and folinic acid in gestational trophoblastic tumours (GTT)

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Summary. Between 1964 and 1986, 487 patients with gestational trophoblastic tumour (GTT) were treated with methotrexate and folinic acid. The patients comprise two groups: between 1964 and 1974, 126 patients were treated but were not systematically stratified using a prognostic score before the start of treatment. These patients formed part of the 317 women who were analysed to identify a number of prognostic variables (Bagshawe 1976). Retrospective analysis of these 126 patients using these prognostic factors showed that in the true low-risk group 85/88 (96%) are alive while 20/22 (91%) of the medium-risk group and only 5/16 (31%) of the high-risk group are alive. Overall the survival was 110/126 (87%) with a minimum follow-up of 14 years. From 1974 all patients were stratified on admission into prognostic groups. Of the true low-risk patients 347/348 survived (99·7%); 13 patients were underscored and treated as low risk when they should have been treated as medium risk, 12 (92%) of these are alive, but nine (69%) needed to change treatment because of drug resistance. While the overall survival in the 1974–1986 group was 359/361 (99%) with a minimum follow-up of 16 months, the survival in all patients (1964–1986) was 469/487 (96%). Although the survival in these patients is excellent it should be noted that 69/348 (20%) low-risk patients had to change treatment because of the development of drug resistance, and a further 23 (6%) needed to change treatment because of drug-induced toxicity. Low-dose methotrexate and folinic acid given in the schedule described remains the treatment of choice in patients with low-risk GTT because of its effectiveness and minimal short- and long-term toxicity. Patients presenting with medium- and high-risk GTT need to start with combination chemotherapy from the outset to avoid the development of drug resistance.

The introduction of methotrexate for the treatment of gestational trophoblastic tumours (GTT) (invasive mole and choriocarcinoma) remains one of the landmarks in the develop-

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ment of cancer chemotherapy. The stimulus to introduce antifolates in this disease arose from the observation by Hertz & Tullner (1949, 1950) on the ability of folate antagonists to block oestrogen-induced tissue growth of genital tissue in animals. This was followed by Thiersch (1952) showing that folic acid antagonists could induce abortion in animals and women.

Li *et al.* (1956) published their initial experience using methotrexate in the treatment of patients with GTT. Methotrexate was clearly a highly active agent in inducing biochemical (in terms of normalization of gonadotrophins) as well as clinical remissions in a substantial number of patients. However, as the early report emphasizes, the optimum schedule of methotrexate administration in this disease was far from clear. In the initial patients with GTT, methotrexate was given either intravenously or orally over several days and led to problems of severe mucositis and myelosuppression, but intermittent treatment with methotrexate was shown to be clinically effective and to have manageable toxicity (Li 1979).

The balance between toxicity and therapeutic effect remained a problem with methotrexate administration. In our early work, methotrexate was used in combination with 6-mercaptopurine and, while this proved a valuable combination for advanced disease (Bagshawe & McDonald 1960), it seemed undesirably toxic for treating disease localized to the pelvis. Methotrexate was then given to the patients with GTT in the pelvis by intra-arterial infusion, and folinic acid rescue was given intramuscularly. This reduced the toxicity from the methotrexate but it was also observed that pulmonary metastases responded to this approach as well as the primary tumour, indicating that the intra-arterial route of methotrexate was not essential to its therapeutic effect (Bagshawe & Wilde 1964).

It was apparent from these studies and other schedules that the important aspects of administration of methotrexate in GTT were: (i) relatively low doses of methotrexate were effective, (ii) folinic acid could prevent methotrexate toxicity if administered between 24 and 48 h of the methotrexate; (iii) rest periods were necessary between courses of methotrexate and folinic acid to prevent major toxicity; and (iv) the intervals between the courses of methotrexate needed to be kept as short as possible to prevent the development of drug resistance and tumour regrowth.

From these observations a standard regimen evolved using methotrexate on days 1, 3, 5 and 7, with folinic acid on days 2, 4, 6 and 8, with rest periods of 6 days between courses (Bagshawe 1969).

These early studies also identified a range of prognostic factors and showed that single-agent treatment with methotrexate and folinic acid was most effective in patients without adverse prognostic factors (Bagshawe 1976) In patients presenting with major adverse prognostic factors, the development of drug resistance to methotrexate is common and these patients need to be managed with combination chemotherapy from the outset. Experience of patients in the medium- and high-risk groups has been recently summarized by Newlands *et al.* (1986) and Begent & Bagshawe (1982).

GTT occurs most commonly after a hydatidiform mole but can also occur after miscarriages and full-term pregnancies. Since patients with hydatidiform mole are at risk of developing GTT, all these patients should be registered for serial human chorionic gonadotrophin (hCG) assays to determine whether or not their disease is regressing. Since 1973 a national registration scheme has been in operation in the UK. Between 1973 and 1983 a total of 8095 patients was registered and only 7·8% required chemotherapy for complications of their disease (Bagshawe *et al.* 1986).

GTT is highly sensitive to a range of therapeutic agents, and some of the early studies of chemotherapy used sequential methotrexate and actinomycin D (Ross *et al.* 1965). However, with the recognition of prognostic factors, low-risk patients could be clearly identified, and it is not necessary to subject the majority of these women to the greater toxicity of actinomycin D (Berkowitz *et al.* 1980, 1982).

Subjects and methods

The patients reported here fall into two groups. The first comprises 126 patients treated between 1964 and 1 January 1974 who received methotrexate and folinic acid in the schedule defined below. These patients were treated before it became routine to stratify patients into low-, medium- and high-risk groups of patients according to the prognostic index shown in Table 1. The second group of patients was treated between 1974 and 1986. These patients form a uniform group in that all these patients were

Table 1. Scoring system for gestational trophoblastic tumours*

	0	1	2	6
Age (years)	<39	>39		
Antecedent pregnancy (AP)	Mole	Miscarriage or unknown	Term	
Interval (end of AP to chemo. at CXH) (months)	<4	4–7	7–12	>12
hCG (iu/l)	10^3–10^4	$<10^3$	10^4–10^5	$>10^5$
ABO blood group (woman×man)		A×O O×A O or A×unknown	B×A or O AB×A or O	
No. of metastases	Nil	1–4	4–8	>8
Site of metastases	Not detected Lungs Vagina	Spleen Kidney	GI tract Liver	Brain
Largest tumour mass (cm)	<3	3–5	>5	
Previous chemotherapy	Nil		Single drug	Two or more drugs

*Low risk=0–5; medium risk=6–9; high risk=>9.
CXH, Charing Cross Hospital, GI tract, gastrointestinal tract.

registered for serial hCG follow-up at the Charing Cross Hospital and were selected for treatment using uniform criteria. The criteria for therapeutic intervention were:

(i) Serum hCG above 20 000 iu/l more than 4 weeks after evacuation (because of the risk of uterine perforation);
(ii) histological evidence of choriocarcinoma;
(iii) metastases in brain, liver or gastrointestinal tract, or radiological opacities >2 cm on chest X-ray;
(iv) long-lasting uterine haemorrhage;
(v) rising hCG values; or
(vi) hCG in body fluids 4–6 months after evacuation.

All patients were treated initially with the following schedule: methotrexate was given intramuscularly (i.m.) in a dose of 50 mg at noon on days 1, 3, 5 and 7. This was alternated with folinic acid, 6 mg i.m., given at 18.00 hours on days 2, 4, 6 and 8. This was followed by 6 rest days before starting the next course. Patients received courses of methotrexate and folinic acid until their hCG concentrations had reached <5 iu/l or until there was evidence of drug resistance or unacceptable toxicity. Those patients achieving normalization of their hCG continued courses of methotrexate and folinic acid until the hCG concentrations had been normal for 8 weeks. In most cases this meant an additional three courses of methotrexate and folinic acid given after the hCG concentration had reached normal.

Patients were followed routinely twice-weekly with serial hCG estimations using a radioimmunoassay with an antibody raised against the beta subunit of hCG. The normal range of this assay is up to 5 iu/l and a limit of detection of 2 iu/l. Patients also had twice-weekly estimations for full blood count for haemoglobin, white cell count and platelet count, urea and electrolytes and liver function tests.

In those patients developing evidence of drug resistance, their therapy was changed to more intensive chemotherapy with sequential etoposide, actinomycin D and vincristine and cyclophosphamide, with methotrexate being omitted from the medium-risk schedule (see Newlands *et al.* 1986).

Results

There were 126 patients treated with methotrexate and folinic acid prior to 1974 (Table 2) before the patients were routinely stratified according to the prognostic factors in Table 1. Although the results in general terms are satisfactory, with an overall survival of 91% and a maximum follow-up of 24 years, lessons have been learned from these figures. In the true low-risk patients (with a score of 0–5 in Table 1), the only deaths out of the 88 patients were not due to drug-resistant GTT. The pulmonary embolism

Table 2. Results in 126 patients treated with methotrexate and folinic acid before 1974

	Prognostic score		
	Low risk (0–5)	Medium risk (6–9)	High risk (>9)
No. of patients	88	22	16†
Changed treatment (%)	11 (12)	6 (27)	8 (50)
Relapsed	4 (4)	4 (18)	1 (6)
Died	3* (3)	2 (9)	11 (69)

*These deaths were not due to the gestational trophoblastic tumour (GTT) but to pulmonary embolus (1), hepatitis (1) and Ewing's sarcoma (1) developing 16 years after treatment for the GTT.

†Six patients had hysterectomy before chemotherapy and four of the five survivors are in this group.

occurred in a patient who had had a hysterectomy immediately before treatment with methotrexate and folinic acid. In the patient who developed a second tumour, it is possible that the previous chemotherapy with methotrexate and folinic acid had increased the risk of the subsequent Ewing's sarcoma. However, in the series overall we have no evidence that methotrexate and folinic acid given in this way increase the risk of second tumours above that in the normal population (Rustin *et al.* 1984).

As shown in Table 2, the need to change treatment from methotrexate and folinic acid increased with the increasing number of risk factors in the patient population. In this group it ranged from 12% in the low-risk to 27% in the medium-risk group and 50% in the high-risk patients. This emphasizes that patients need to be carefully stratified at the start of treatment. In this disease the development of drug resistance with a mortality in the high-risk subgroup of 69% is unsatisfactory.

All patients with GTT have been routinely stratified using prognostic factors since 1974 and all patients treated until 1986 have been analysed. Review of the scoring of each individual patient indicated that clinical errors or subsequent additional information resulted in incorrect scoring in 13 out of 361 patients (Table 3). In the patients who were truly at low risk there was only one death out of 348 patients and this was due to concurrent (not therapy-induced) non-Hodgkin's lymphoma. The relapse rate was low (4%), but it is important to recognize that methotrexate and folinic acid in true low-risk patients will still fail to eliminate the disease in 20% due to the development of drug resistance. In addition to the patients who developed drug resistance, there were 23 (6%) who needed to change treatment because of toxicity from methotrexate and folinic acid (severe mucositis, severe pleuritic chest pain, drug rash and evidence of hepatic toxicity). Therefore on this schedule 26% of patients will need to change treatment either because of drug resistance or therapy-related toxicity In both groups there were two deaths from hepatitis. The first patient developed hepatic failure at the end of treatment with methotrexate and folinic acid. The second patient was known to be hepatitis B antigen positive and

Table 3. Results in 361 patients treated with methotrexate and folinic acid between 1974 and 1986

	Prognostic score		
	Low risk (0–5)	Medium risk (6–9)	High risk (>9)
No. of patients	348	13	0
Changed treatment for drug resistance (%)	69 (20)	9 (69)	0
Relapsed	13 (4)	2 (15)	0
Died	1*	1 (8)†	0

*Patient died from concurrent non-Hodgkin's lymphoma.

†Patient died from hepatitis.

Table 4. Survival of all patients treated with methotrexate and folinic acid

	Prognostic score				
	Low risk (0–5)	Medium risk (6–9)	High risk (>9)	Total	Grand total (all patients)
No. of patients before 1974 (survival %)	85/88 (96%)	20/22 (91%)	5/16 (31%)	110/126 (87%)	469/487 (96%)
No. of patients 1974–1986 (survival %)	347/348 (99·7%)	12/13 (92%)	—	359/361 (99%)	

went into hepatic failure after multidrug therapy after her GTT relapsed. Both deaths could have been related to hepatitis B or chemotherapy or to a combination of the two.

There were 13 patients who were incorrectly scored and on review fell into the medium-risk category; 69% of these were required to change treatment because of drug resistance. These results show that the prognostic variables that were identified from the patients treated before 1974 also apply to this prospective group. In Table 4 both groups are combined to give the overall survival. Clearly, with a 94% survival rate with a follow-up ranging from 24 years to 16 months, this subgroup of GTT remains the most curable of human tumours with cytotoxic chemotherapy. Illustrations of serial hCG estimations in the management of these patients are shown in Fig. 1 in a patient going into remission on methotrexate and folinic acid, and in Fig. 2 in a patient developing drug resistance and requiring a modification in her treatment.

In Fig. 3 the mode for duration of chemotherapy in patients completing treatment on methotrexate and folinic acid was 12 weeks, and in the group who were required to change treatment because of evidence of drug resistance the mode was 18 weeks. We do not feel that this

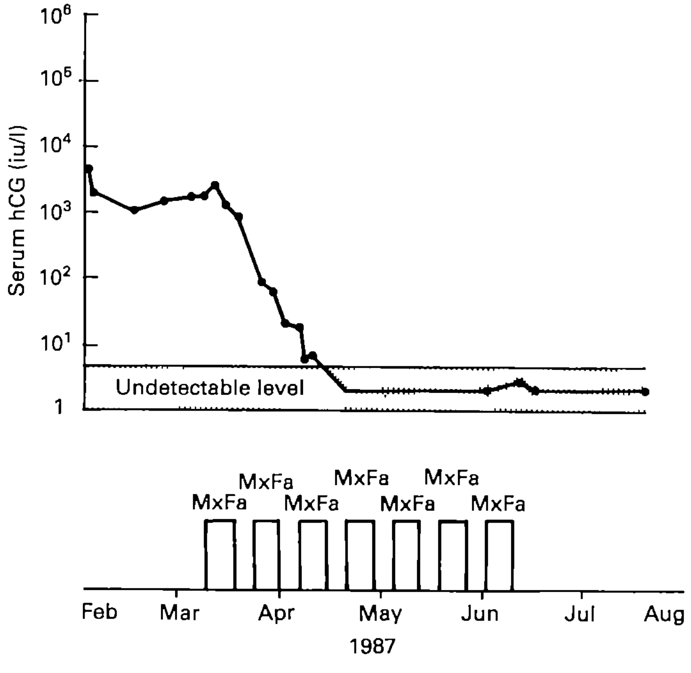

Fig. 1. Serial hCG estimations in the management of a 25-year-old patient with post-molar trophoblastic disease, prognostic score 3, who went into remission on methotrexate (Mx) and folinic acid (Fa).

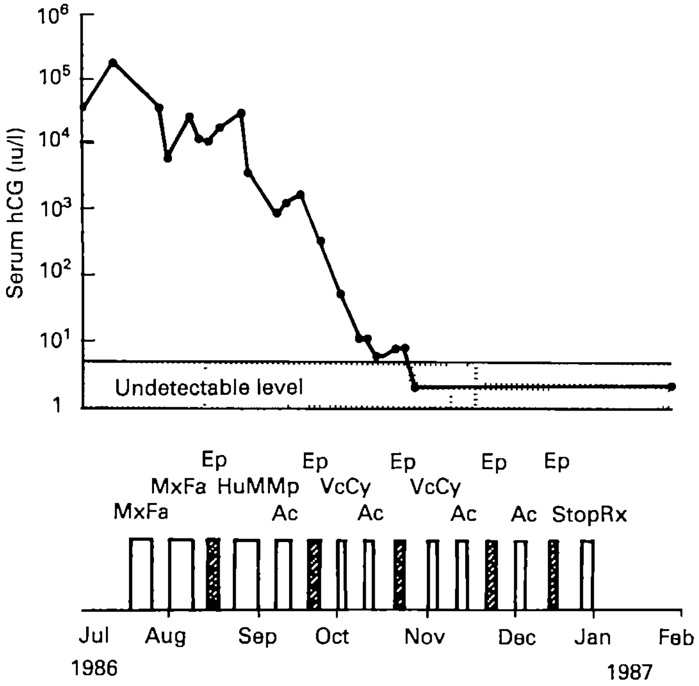

Fig. 2. Serial hCG estimations in the management of a 26-year-old patient with post-molar trophoblastic disease, prognostic score 3, who developed drug resistance and required a modification in her treatment. Mx, Methotrexate; Fa, folinic acid; Ep, etoposide; HuMMp, hydroxyurea, methotrexate, 6-mercaptopurine; Ac, actinomycin D; VcCy, vincristine and cyclophosphamide.

increase of 6 weeks duration in treatment is sufficient to warrant modifying the policy of starting all true low-risk patients on methotrexate and folinic acid.

Discussion

We still regard methotrexate and folinic acid as the treatment of choice for patients with GTT falling into the low-risk group, for the following reasons: (i) toxicity in the majority of patients is minimal and little alopecia is induced; (ii) once the disease has gone into remission in terms of consistently normal hCG estimations the treatment can be completed at home, given by the district nurse; (iii) to date there has been no evidence that methotrexate and folinic acid impairs subsequent fertility (Rustin *et al.* 1984); and (iv) there is no evidence that methotrexate is carcinogenic when given in this way (Rustin *et al.* 1987). However, it has to be clearly recognized that one-quarter of these patients will need to modify their treatment either because of the

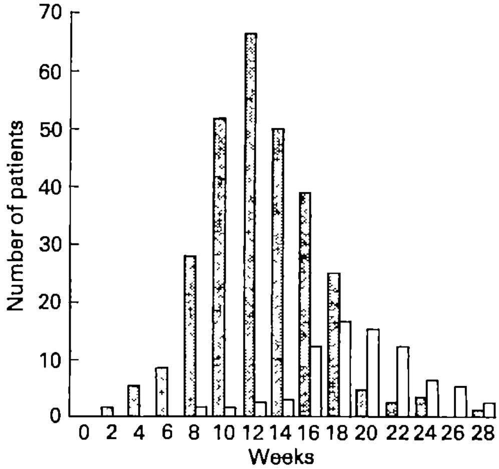

Fig. 3. Duration of treatment for patients treated for low-risk GTTs. ▨, Patients successfully treated with methotrexate/folinic acid; □, patients who were required to change treatment because of drug resistance.

development of drug resistance (20%) or because of unacceptable side-effects from the chemotherapy (6%).

The schedule of administration of methotrexate is probably also important in this disease. In the 1970s we performed a pilot study of higher dose methotrexate (300 mg/m^2 i.v. weekly followed by folinic acid at 24 h) in a group of patients with low-risk GTT. We were surprised when the frequency of drug resistance rose from the 20% identified here to 53% (8/15 patients). Although this was not a randomized study, clinically no other cause for this high proportion with drug resistance was identified in this group of patients except the change in schedule of methotrexate. Interestingly, in this group receiving higher dose methotrexate, pleuritic chest pain was not observed although this is a well-recognized complication of the standard 8-day schedule with methotrexate and folinic acid given on alternate days. This unsuccessful attempt to try and modify the administration of methotrexate takes us back to the early scheduling of methotrexate in the 1950s and 1960s. In GTT it appears likely that the duration of exposure of the trophoblastic tumour cells to methotrexate is more important than the concentration of methotrexate in eliminating this disease.

Petrilli *et al.* (1987) have recommended that actinomycin D given intravenously at a dose of 1·25 mg/m^2 every 2 weeks should be regarded as the treatment of choice for patients falling into the low-risk category. This dose of actinomycin D will induce moderate to severe nausea and vomiting in the majority of adults. In this series of 31 patients, 84% experienced nausea and vomiting. Adults do not tolerate repeated doses of actinomycin D well, in addition to the other toxicities of alopecia, myelosuppression and skin rashes. There is no doubt that actinomycin D is an active agent in relation to GTT but we would recommend that this DNA intercalating agent should be reserved for patients falling into the medium- and high-risk groups. In patients with an excellent prognosis it must be of concern to oncologists that there may be long-term side-effects from the therapy. We have already observed two patients developing acute myeloid leukaemia after extensive and prolonged chemotherapy for high-risk GTT (one patient received methotrexate, cyclophosphamide, actinomycin-D, adriamycin, vincristine, hydroxyurea, etoposide and cis-platinum over 13 months, and the second patient received etoposide, methotrexate, actinomycin-D, vincristine and cyclophosphamide over 7 months). Except where drug costs are of prime importance, we disagree with the recommendation to use actinomycin D as the initial therapy in this group of patients.

We originally identified the very high degree of activity of etoposide in GTT in 1977 (Newlands & Bagshawe 1980; Hitchins *et al.* 1988) and have subsequently integrated this drug in the treatment of medium- and high-risk patients (Newlands *et al.* 1986). But, although etoposide is subjectively a well-tolerated drug, the main problems associated with it are almost total alopecia and occasional severe allergic reactions as well as the predictable myelosuppression. We have found no evidence that etoposide impairs the subsequent fertility of women with GTT (Adewole *et al.* 1986). However, there is so far only 11 years experience of this drug in the context of a highly curable disease, which is still relatively early to detect any potential carcinogenicity. We have therefore felt that etoposide is also an inappropriate drug to use as a first-line agent in patients with low-risk GTT Wong *et al.* (1986) have reported very good results in a series of 60 patients with GTT treated with oral etoposide therapy in terms of remission of tumour and a relatively low relapse rate of 5%, but they have confirmed that etoposide can suppress ovarian function (Choo *et al.* 1985).

While we are pleased to have this independent confirmation of the very high degree of activity of etoposide in GTT, we would not agree with their conclusion that etoposide should be used in all patients as a primary agent. The results reported here in this large series of patients clearly show that even with its defects and limitations methotrexate with folinic acid can eliminate low-risk GTT with minimal side-effects in 74% of patients. We think that in view of the known side-effects of etoposide and the unknown long-term potential side-effects of this agent, it should be reserved for patients where either methotrexate resistance has developed or the patients initially fall into the medium- and high-risk groups.

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A comparison of fetal abdominal circumference measurements and Doppler ultrasound in the prediction of small-for-dates babies and fetal compromise

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Summary. A total of 145 pregnancies clinically suspected of being small-for-dates was studied at presentation with a single measurement of the fetal abdominal circumference and Doppler studies of the umbilical and arcuate arteries. The abdominal circumference measurement gave the best prediction of the small-for-gestational-age (SGA) baby (sensitivity 73%, umbilical artery sensitivity 47%, arcuate artery sensitivity 29%). The umbilical artery measurement gave the best prediction of antenatal fetal compromise; the performance of the tests was compared for a fixed sensitivity of 100% (i.e. all cases of antenatal compromise would be detected), the specificity of the umbilical artery measurement was 77%, abdominal circumference measurement 12% and arcuate artery measurement 2%. In our data, umbilical artery studies were not a sensitive predictor of the SGA baby but they did give an accurate prediction of the potentially compromised SGA fetus.

The implications of intrauterine growth retardation (IUGR) are well recognized. Perinatal mortality is 4–10 times higher than in babies who are appropriately grown, and growth-retarded babies are at risk of perinatal complications which may result in later neurodevelopmental disability (Chiswick 1985). Considerable energy is therefore directed towards the antenatal detection of these babies. Standard methods of diagnosis are based on assessment of fetal size, symphysis–fundal height measurements and ultrasound fetal measurements (Pearce & Campbell 1987) thus selecting a group who are considered to be small-for-gestational-age (SGA) for further investigation and fetal monitoring. However, SGA fetuses are a heterogeneous group, including those that are constitutionally small but normal, as well as those whose intrauterine growth is pathologically impaired. Not all these small babies are at risk, it is the group where uteroplacental insufficiency is thought to play an important part in which detection and appropriate intervention should lead to a reduction in perinatal mortality and morbidity (RCOG 1984). An asymmetrical pattern of growth retardation

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on serial ultrasound measurements (Campbell & Thoms 1977) may help to identify these babies, but nevertheless standard methods of detection based on assessment of fetal size inevitably result in unnecessary investigation and monitoring of many pregnancies where the outcome is normal.

Doppler ultrasound studies appear to have considerable potential in the assessment of fetuses suspected of IUGR. The normal placenta is a low-resistance vascular structure which is reflected in the high diastolic flow seen in the normal umbilical artery flow velocity waveform (FVW). Early reports described the positive association between abnormal waveforms, characterized by reduction in end-diastolic flow secondary to increased placental vascular resistance, and IUGR (Reuwer *et al.* 1984; Erskine & Ritchie 1985; Trudinger *et al.* 1985*a*; Fleischer *et al.* 1985). More recent work has focused on the recognition of fetal compromise and the ability of the umbilical artery FVW to discriminate between those SGA fetuses at risk of perinatal complications and those where the outcome is normal (Trudinger *et al.* 1985*b*; Reuwer *et al.* 1987; Rochelson *et al.* 1987; Laurin *et al.* 1987; Haddad *et al.* 1988).

Doppler studies of the maternal side of the placental circulation may yield further information. Studies of branches of the uterine artery (arcuate arteries, Campbell *et al.* 1983) have been advocated as a screening test in the early second trimester for the identification of high-risk pregnancies (Campbell *et al.* 1986), and abnormal signals are associated with an increased rate of pregnancy-induced hypertension, poor fetal growth and fetal hypoxia (Campbell *et al* 1983; Trudinger *et al.* 1985*c*; Fleischer *et al.* 1986).

The aim of this paper is to compare the clinical value, at presentation, of a single ultrasound measurement of the fetal abdomen, single umbilical artery FVW and single arcuate artery FVW in the prediction of the SGA baby and fetal compromise in a group of patients who are selected for investigation because of the clinical suspicion of IUGR.

Patients and methods

The study group comprised 145 patients in the third trimester who were, on the basis of clinical assessment, thought to have a small-for-dates fetus; 51 had hypertensive disorders, and in the other 94 there was no obvious pregnancy complication. Patients were studied at presentation, with a single measurement of the fetal abdominal circumference, and FVW were obtained from the umbilical and arcuate arteries; all studies were completed within 7 days.

Ultrasound measurements were performed in the standard manner (Campbell & Wilkin 1975) using a 3·5-MHz linear array (Picker LS 7000, G.L.Z. series). Doppler studies were performed using a continuous wave system (Doptek 4-MHz transducer with spectrum analyser, filter level 150 Hz). Waveforms of the umbilical artery were only accepted if a clear venous signal was visible in the reverse channel. Arcuate artery signals were obtained from the lower left and right abdomen and recognized by the maternal heart rate and characteristic waveform profile with low pulsatility and high diastolic flow. All signals were recorded on to an audio-cassette and analysed later by an operator who was unaware of the clinical outcome. The mean resistance index (RI) (Pourcelot 1974) of at least five technically acceptable waveforms was taken. In extremely abnormal waveforms where no diastolic flow was seen above the filter level, the RI was called 1·0. For the arcuate artery the mean of the two values was taken as the test result.

The clinicians were not informed of the Doppler study results, thus intervention was carried out on the basis of traditional obstetric management. The case notes of all these patients were analysed by one of us who was unaware of the ultrasound and Doppler results. Three outcome groups were defined: babies with birthweight < the 10th centile (birthweight centiles calculated with corrections made for sex and maternal parity, Altman & Coles 1980); babies with evidence of antenatal fetal compromise, defined as the occurrence of an ominous antenatal cardiotocogram prompting caesarean section (Flynn *et al.* 1979), and babies with birthweights >10th centile and no evidence of fetal compromise.

A reference range for both the umbilical artery RI and the arcuate artery RI for different gestations was derived from normal pregnancies.

Statistical methods

Values of the fetal abdominal circumference were corrected for gestation and expressed as multiples of the standard deviation relative to the mean of a normal reference range (Campbell & Thoms 1977). In normal pregnancy the umbilical artery RI decreases with advancing gestation (Trudinger *et al.* 1985*a*) and these values were

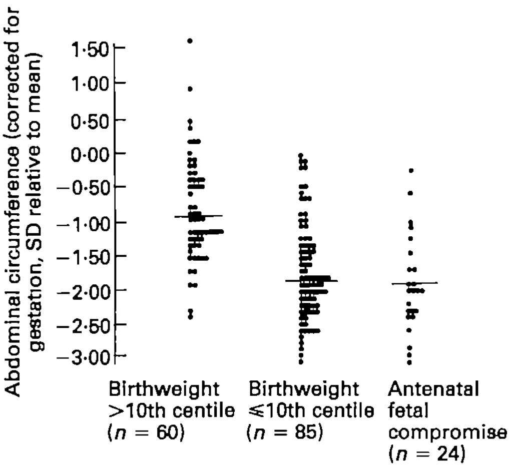

Fig. 1. Results of the fetal abdominal circumference measurements, the horizontal bar indicates the mean for each group.

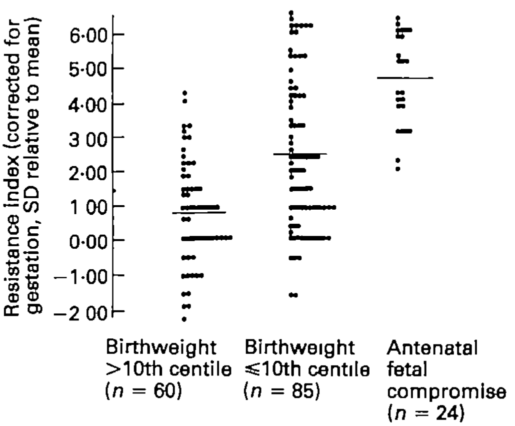

Fig. 2. Results of the umbilical artery studies, the horizontal bar indicates the mean for each group.

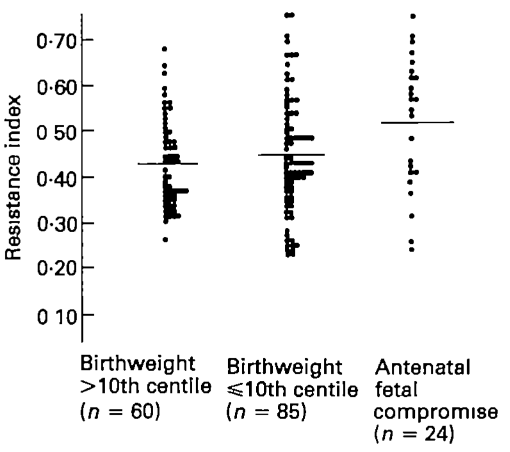

Fig. 3. Results of the arcuate artery studies, the horizontal bar indicates the mean for each group.

therefore also corrected for gestation and expressed as multiples of the standard deviation relative to the mean of our normal series Arcuate artery indices are constant in the third trimester in normal pregnancies (Pearce 1987) and therefore no correction was necessary.

The association between pregnancy outcome and the fetal abdominal circumference, umbilical and arcuate artery RI was investigated using the unpaired *t*-test.

Receiver operating characteristic (ROC) curves (Richardson *et al.* 1985) were drawn to demonstrate the sensitivity and specificity of the tests over a range of thresholds. For the outcome birthweight <10th centile, comparison was made between tests for a fixed specificity of 80%, this was chosen as an acceptable level at which to operate the test clinically. For the outcome antenatal fetal compromise, comparison was made between tests for a fixed sensitivity of 100%. This was chosen because antenatal fetal compromise is a serious condition which may result in intra-uterine death and it is therefore important to identify all these pregnancies. Differences in sensitivity and specificity for the two outcomes were tested using the McNemar's test (Armitage & Berry 1987*a*).

Logistic regression (Armitage & Berry 1987*b*) was then used to investigate whether a combination of tests performed better than each individual test.

Results

Gestational age ranged from 28 to 39 weeks with a mean of 35 weeks (SD 3·2), 83 (57%) women were nulliparous, 67 (46%) were smokers.

Results of the abdominal circumference measurements and umbilical and arcuate artery studies are given in Figs 1, 2 and 3. The mean abdominal circumference was lower in those women who gave birth to babies with birthweight <10th centile (SD −1·72, *P*<0·001) and in those with evidence of antenatal fetal compromise (SD −1·86, *P*<0·001). The umbilical artery RI was significantly higher in those women who gave birth to babies with birthweights <10th centile (SD 2·38, *P*<0·001) and in those with evidence of antenatal fetal compromise (SD 4·8, *P*<0·001). There was no significant difference in the mean arcuate artery RI between the group with birthweights >10th centile (0·43) and the group with birthweights <10th centile (0·45); however, the mean RI was significantly higher (0·52, *P*<0·01)

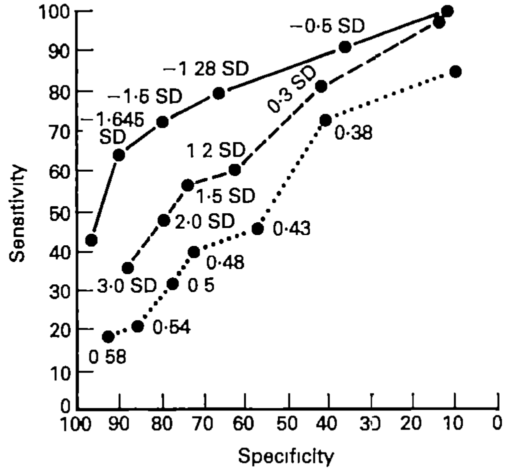

Fig. 4. ROC curves for the outcome birthweight <10th centile, cut-off levels are marked on the curves. ———, Abdominal circumference; – – –, resistance index umbilical artery; . . . ., resistance index arcuate artery.

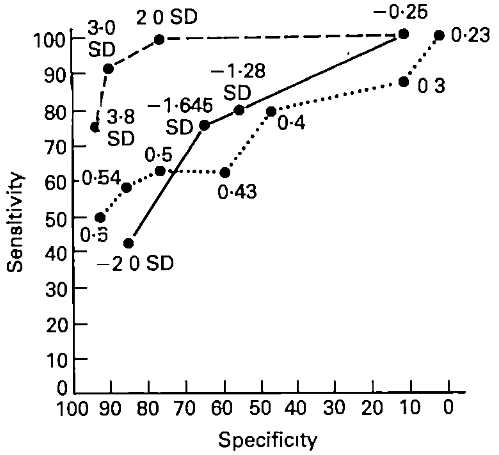

Fig. 5. ROC curves for the outcome antenatal fetal compromise, cut-off levels are marked on the curves. ———, Abdominal circumference; – – –, resistance index umbilical artery; . . . ., resistance index arcuate artery.

in those pregnancies with evidence of antenatal fetal compromise.

Birthweight < the 10th centile

Overall 85 women (58%) gave birth to SGA babies (<10th centile birthweight) and 66 of them (78%) gave birth to babies <5th birthweight centile. Of the 60 babies with birthweights > the 10th centile 43 (72%) had a birthweight between the 10th and 25th centiles

ROC curves are shown in Fig. 4. Table 1 gives the sensitivity of each test at a fixed specificity of 80%. The measurement of abdominal circumference gives the highest sensitivity (73%) of the three tests taken individually. This is significantly higher than the umbilical artery RI (47%, $P<0{\cdot}001$) and arcuate artery RI (29%, $P<0{\cdot}001$).

Logistic regression showed that both the umbilical RI (RI UA) and abdominal circumference (AC) are significantly associated with low birthweight. The combined score is 0·36 × RI UA − 1·17 × AC. However, use of the combined score did not give significantly different sensitivities (78%, $P = 0{\cdot}92$).

Antenatal fetal compromise

Twenty-four patients had evidence of antenatal fetal compromise, this included two stillbirths and in addition there were two neonatal deaths in the group.

ROC curves are shown in Fig. 5. Table 2 gives

Table 1. Outcome birthweight <10th centile. Characteristics of tests assuming a fixed specificity of 80%

Measurement	Cut-off	Sensitivity	Predictive value Positive	Predictive value Negative	*P* (comparison of sensitivity with AC)
AC	−1 5 SD	73%	84%	67%	—
RI UA	2·0 SD	47%	77%	52%	<0·001
RI AA	0·5	29%	66%	44%	<0·001
Combined RI UA and AC	2·08	78%	85%	72%	0·92

AC, Abdominal circumference; RI UA, resistance index umbilical artery; RI AA, resistance index arcuate artery.

Table 2. Outcome antenatal fetal compromise. Characteristics of tests assuming a fixed sensitivity of 100%

Measurement	Cut-off	Specificity	Predictive value		*P* (comparison of specificity with umbilical artery RI)
			Positive	Negative	
AC	−0·2 SD	12%	18%	100%	<0·001
RI UA	2·0 SD	76·8%	46%	100%	—
RI AA	0·24 SD	1·6%	17%	100%	<0·001
Combined score					
RI UA/RI AA	7·0	77·7%	47%	100%	>0·9

For abbreviations see Table 1.

the specificity of each test for a fixed sensitivity of 100%. The umbilical artery RI gives the highest specificity (76·8%) of the three tests taken individually. This is significantly higher than the arcuate artery RI (1·6%, $P<0{\cdot}001$) and abdominal circumference (12%, $P<0{\cdot}001$).

Logistic regression showed that both the umbilical and arcuate artery RI were significantly associated with antenatal fetal compromise, the combined score is 1·5 × RI UA + 8·3 × RI AA. However, use of the combined score did not give a significantly different specificity (Table 2).

Conclusions

In this study ultrasound measurement of the fetal abdominal circumference was the best predictor of the SGA baby. Ultrasound measurements may be used to make an assessment of fetal size or serially to monitor fetal growth. In this study we have assessed ultrasound when used in the former way in a group of patients who present for the first time and are clinically suspected of being small-for-dates. A single abdominal circumference measurement in the third trimester has been reported to detect about 85% of fetuses whose subsequent birthweight was <10th centile (Warsof *et al.* 1983; Neilson *et al.* 1980). The sensitivity of the ultrasound measurement was lower in this study, but the accuracy of ultrasound predictions is greatest when performed close to delivery (Little & Campbell 1982), and in this study the interval between presentation and delivery ranged from 1 to 11 weeks.

But birthweight is not of prime importance; the aim of antenatal surveillance is to identify a group of SGA fetuses at risk of intrauterine death and perinatal asphyxia, where uteroplacental insufficiency is thought to be an important aetiological factor. Doppler studies provide a non-invasive method for study of placental blood flow, and in this study the umbilical artery RI gave an accurate prediction of antenatal fetal compromise; other workers have reported similar findings (Trudinger *et al.* 1985*b*; Reuwer *et al.* 1987; Rochelson *et al.* 1987; Laurin *et al.* 1987; Haddad *et al.* 1988). The arcuate artery RI was also associated with fetal compromise but was a less sensitive predictor than the umbilical artery RI. Again other workers have reported similar findings (Trudinger *et al.* 1985*b*). The umbilical artery RI was superior to the fetal abdominal circumference measurement in the detection of the compromised fetus with IUGR. This is to be expected given the heterogeneous nature of the SGA fetuses, many of whom will be small due to genetic factors rather than any pathological process. In this study, patients were studied at presentation, and abnormalities in the umbilical artery FVW preceded abnormalities in the CTG by between 2 and 35 days, thus giving a long-term warning of fetal risk.

In conclusion, it would appear that Doppler studies of the umbilical artery are not strongly associated with low birthweight for gestational age but are a very sensitive predictor of antenatal fetal compromise and are superior to standard ultrasound fetal measurements and arcuate artery studies in the detection of the potentially compromised SGA fetus.

Acknowledgments

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The diagnosis of polycystic ovaries in subfertile women

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Summary. Laparoscopy was used to identify the polycystic ovary (PCO) in a group of subfertile women. A third were found to have PCO. These patients had higher levels of luteinizing hormone (LH), testosterone (T) and a higher free androgen index (FAI) than those with normal ovaries. Only 15% of patients with laparoscopic evidence of PCO were obese, hirsute and oligomenorrhoeic. Within the PCO group, hirsutism was strongly associated with obesity and a high FAI. A group of subfertile women with PCO and regular cycles was found who had no other identifiable cause for their infertility. These women had higher follicular phase concentrations of LH and higher FAI than ovulatory women with normal ovaries.

The polycystic ovary (PCO) is usually enlarged with a thickened, smooth capsule, increased stroma and multiple, peripheral small follicles (Stein & Leventhal 1935; Goldzieher & Green 1962). An accurate diagnosis can be made by laparoscopic inspection of the ovary and, more recently, by use of high resolution ultrasound (Adams *et al.* 1986; Conway & Jacobs 1987; Eden *et al.* 1988*a*; Eden 1988). The PCO may be found in women with symptoms such as obesity, oligo-amenorrhoea or hirsuties (Goldzieher & Green 1962; Adams *et al.* 1986; Eden *et al.* 1988*a*), although recently it has been suggested by Polson *et al.* (1988) that as many as 23% of normal women may have ovaries with the ultrasound appearance of PCO. It is possible that women with polycystic ovaries may have a hypersensitive hypothalamic–pituitary–ovarian axis, rendering them prone to menstrual disturbances and the abnormal secretion of androgens when 'stressed' by extra-gonadal factors such as obesity (Eden 1988). Excess androgen secretion, often associated with the PCO, is not always clearly ovarian in origin (Yen 1980). It is possible that in some women the initial event is an excess secretion of adrenal androgens (Yen 1980) which then transform a normal ovary into the polycystic type. Exogenous androgens given to patients undergoing gender reassignment surgery produce histological changes similar to those found in PCO (Amirikia *et al.* 1986).

The free androgen index (FAI) is an index of free testosterone (T) activity (Carter *et al.* 1983) and we have found the FAI to be a useful test for detecting patients with PCO in a group with oligomenorrhoea (Eden *et al.* 1988*a*; Eden 1988).

Sex hormone binding globulin (SHBG) binds T preferentially and more avidly than oestradiol (Burke & Anderson 1972). Hepatic production of SHBG falls in the presence of excess androgen and such a fall in SHBG will increase free T activity (Anderson 1974). Low levels of SHBG are associated with PCO and obesity (Eden *et al.* 1988*a*, 1988*b*; Cunningham *et al.*

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1985). In this study, laparoscopy and ultrasound were used to inspect the ovaries in a group of infertile women, and the FAI was employed as a biochemical indicator of free T activity, to investigate the endocrine correlates of a visual diagnosis of PCO in a group of women attending an infertility clinic.

Subjects and methods

Subjects consisted of 206 consecutive women undergoing diagnostic laparoscopy for the investigation of infertility of at least 12 months duration. All the laparoscopies were performed by the same surgeon (J.A.E.). Overall 95% of the patients attending the Infertility Clinic, Charing Cross Hospital, had a laparoscopy over this period of time. A 'double puncture' technique under general anaesthesia was used. In addition to the usual subumbilical incision for the introduction of the laparoscope, a second puncture was made to allow the introduction of grasping forceps. This permits the surgeon to grasp the ovarian ligament and lift the ovary out of the pelvis to allow adequate inspection. The methods used for laparoscopy, ultrasound and biochemistry have been described previously (Eden *et al.* 1988*a*, 1988*b*; Eden 1988). Patients with regular cycles had blood collected in the early follicular phase. Where possible, oligomenorrhoeic patients were sampled during a spontaneous menstrual period. All subjects had the following measured: follicle-stimulating hormone (FSH), LH, T, SHBG and prolactin (PRL). The FAI was calculated by using the formula T × 100/SHBG (Carter *et al.* 1983; Eden *et al.* 1988*a*). LH, FSH, PRL and T were measured by conventional radioimmunoassay. SHBG was measured by the two-tier column method described by Iqbal & Johnson (1977). The between-batch coefficients of variation (means in parentheses) for the laboratory assays were: LH 8·6% (7·8 U/l), FSH 7·3% (4·6 U/l), PRL 10·1% (536 mU/l), T 10·8% (3·1 nmol/l) and SHBG 11·4% (23·5 nmol DHT bound/l). The early follicular phase reference range for our laboratory is as follows: LH 1·5–9·8 U/l, FSH 0·2–7·4 U/l, PRL < 800 mU/l, T 1·0–2·6 nmol/l, SHBG 31–107 nmol DHT/l and FAI 1·0–4·5.

Patients were asked to keep menstrual records and most kept basal body temperature charts (BBT). A 'regular cycle' was defined as a cycle length of 22 to 36 days with ovulatory luteal phase progesterone levels (>30 nmol/l) and usually a biphasic BBT. 'Oligomenorrhoea' was defined as fewer than eight cycles per year with a flat BBT or low progesterone. Subjects were examined for hirsuties, namely the presence of terminal hair on the face, chest, midline abdomen or thigh. No grading system was used for this study. Most of our patients were Anglo-Saxon Caucasians. Body-mass index (BMI) was calculated as weight/height^2 (kg/m^2). Obesity was defined as >25 kg/m^2. The male partners were asked to produce a sample of semen for analysis (within 2 h of collection), and if an abnormality was found then the test was repeated. Our laboratory considers a sperm count of <20 million/ml or <60% motile or <60% normal forms as an abnormal result. Postcoital tests (PCT) were performed in the late follicular phase in those patients with regular cycles. The test was considered normal if more than five active sperm were seen per high-power field. If the PCT was not normal, it was repeated on two more occasions.

Some couples were referred to other institutions for more sophisticated tests of sperm function and sperm–mucus interaction and most had hysterosalpingography. These results are not given as these tests were not systematically applied and are not strictly relevant to this paper.

We consider the PCO to be a morphological diagnosis based on surgical or ultrasound findings. The ultrasound criteria for PCO used by our department are those described by Adams *et al.* (1986), namely the presence of more than 10 small peripheral follicles and increased echogenic stroma. The ovarian volume is usually >6 ml. We define the PCO syndrome as a patient with PCO and symptoms such as subfertility, oligo-amenorrhoea, dysfunctional uterine bleeding or hirsutism.

All women with PCO and 65 women with laparoscopically normal ovaries also had an ultrasound scan on at least one occasion as described previously (Eden *et al.* 1988*a*). The sonographer was not given the laparoscopic diagnosis. In four women it was not possible to see the left ovary because of overlying bowel. All 65 patients with laparoscopically normal ovaries were found to be sonographically normal. Ultrasound correctly diagnosed 66 of the 68 patients with PCO. In addition, all 16 women with PCO and regular cycles had serial ultrasound scans throughout one cycle and in each one ovulation was reported by the usual criteria (Hackloer & Sållman 1983).

Results were compared using the Mann–Whitney U-test. The linear regression equation and the correlation coefficient (r) were used to examine the relation between sets of data (LH and FAI were log transformed before calculating r, to normalize their distributions). The significance of r and differences in percentages were compared using Student's t-test.

Results

It was possible to classify patients into four groups on the basis of menstrual data and ovarian appearance: (1) Normal ovaries and regular cycles ($n = 122$); (2) normal ovaries and oligomenorrhoea ($n = 16$); (3) PCO and regular cycles ($n = 16$); and (4) PCO and oligomenorrhoea ($n = 52$).

The diagnoses for the patients with oligomenorrhoea and normal ovaries are given in Table 1.

The hormone levels of the four patient categories have been analysed after subdivision into those with normal and polycystic ovaries (Table 2, Fig. 1). Analysis of the results has been divided into two sections.

Patients with normal ovaries

Oligomenorrhoeic women with normal ovaries were thinner than the women with regular cycles (Fig. 1). Testosterone was significantly lower in these oligomenorrhoeic women, but no difference was found for FSH, PRL, SHBG or FAI (Table 2, Fig. 1). No oligomenorrhoeic woman with normal ovaries had a FAI> 4·5. Only 4 (3%) of women with regular cycles had a high FAI. Each of them had a BMI> 30 kg/m^2. There was a significant relation between FAI and BMI ($r = 0{\cdot}43$, $P<0{\cdot}001$, Fig. 2) and a significant negative relation between SHBG and BMI ($r = -0{\cdot}28$, $P<0{\cdot}01$). Log LH was not significantly correlated with T or FAI, nor was there a relation between T and BMI or BMI and age. FAI was negatively correlated with age ($r = -0{\cdot}40$, $P<0{\cdot}001$) although there was no significant relation between either T or SHBG and age. SHBG was negatively correlated with T ($r = -0{\cdot}30$, $P<0{\cdot}001$).

Table 1. Diagnoses in the oligomenorrhoeic patients with normal ovaries

Diagnoses	n	(%)
Weight loss (and BMI <20 kg/m^2)	5	(31)
Thyroid disease	2	(12·5)
Hyperprolactinaemia	2	(12·5)
Elevated gonadotrophins	2	(12·5)
Hypogonadotrophic hypogonadism (and no weight loss)	2	(12·5)
Unknown	3	(19)
Total	16	(100)

Patients with PCO

Oligomenorrhoeic women with PCO had significantly higher serum levels of LH, T, a higher FAI and lower SHBG concentrations than women with PCO and regular cycles (Table 2, Fig. 1). All oligomenorrhoeic women with PCO had a FAI> 4·5, compared with 19% of those with regular cycles ($P<0{\cdot}001$). Considering all patients with regular cycles, those with PCO had higher concentrations of LH, T, a higher FAI and lower SHBG than those with normal ovaries (Table 2, Fig. 1). Women with PCO and regular cycles had otherwise normal laparoscopies, normal PCT, partners with normal semen analyses, and appear to have endocrine features between those of oligomenorrhoeic women with PCO and women with regular cycles and normal ovaries. Hirsute women with PCO had a higher median BMI (26) than their non-hirsute counterparts (23) ($P<0{\cdot}001$). Of the hirsute women 73% were obese, compared with only 2% of the non-hirsute women ($P<0{\cdot}001$). Compared with non-hirsute women, hirsute women had a higher median FAI (7 and 11 respectively, $P<0{\cdot}03$), a higher median T level (2·5 and 3·2 nmol/l respectively, $P<0{\cdot}05$) and lower median SHBG concentration (38 and 24 nmol DHT/l respectively, $P<0{\cdot}05$). No significant difference was found for LH, FSH, PRL or the risk of oligomenorrhoea. Both patients with normal and PCO demonstrated a significant correlation between the FAI and BMI, but the regression slope was steeper for the patients with PCO (Fig. 2). In the group with PCO, SHBG concentration was negatively correlated with BMI ($r = -0{\cdot}45$, $P<0{\cdot}001$), but there was no significant relation between T and BMI. T was correlated with log LH ($r = 0{\cdot}32$, $P<0{\cdot}001$), but not with BMI. As in normal women, LH and FSH were correlated ($r = 0{\cdot}56$,

Table 2. Hormone results in the four subgroups

	Normal ovaries		Polycystic ovaries	
	Regular cycles	Oligomenorrhoea	Regular cycles	Oligomenorrhoea
n	122	16	16	52
Age (years)	31 (21–42)	33 (28–41)	31 (20–40)	31 (17–39)
FSH (U/l)	3·4 (0·7–8·6)	4·1 (2·9–28·0)	3·9 (2·1–7·4)	3·9 (1·1–7·6)
T (nmol/l)	1·7 (1·1–2·5)	1·3** (0·8–2·0)	2·0* (1·0–3·2)	2·5** (1·2–5·3)
SHBG (nmol DHT/l)	67·5 (31–120)	56 (40–118)	56* (23–110)	33***(6–76)
PRL (mU/l)	315·5 (85–1083)	276 (65–1400)	285 (85–740)	265 (46–1030)

*$P<0{\cdot}05$, **$P<0{\cdot}005$, ***$P<0{\cdot}001$.

Each column is compared with the preceding column, except for PCO patients having regular cycles, who are compared with subjects with regular cycles and normal ovaries

Results are median values with range in parenthesis.

$P<0{\cdot}001$) and the FAI was not correlated with increasing age, as it was in normal women.

The discriminatory ability of the hormone tests and pelvic ultrasound to diagnose the PCO is shown in Table 3.

Discussion

In this study, 95% of patients attending an infertility clinic had a laparoscopy and 33% of them were found to have PCO. Only 15% of our subjects with PCO were obese, hirsute and oligomenorrhoeic. We consider the PCO to be a morphological diagnosis, and if we had relied on this triad of symptoms alone we would have missed 85% of cases. Direct inspection (with or without biopsy) of the ovaries must be considered the reference test for the diagnosis of PCO. However, ultrasound holds much promise (Adams *et al.* 1986; Eden *et al.* 1988*a*; Eden 1988). The serum levels of T, LH and SHBG found in our group with PCO were similar to those found in other series (Adams *et al.* 1986; Conway & Jacobs 1987; Yen 1980), but relatively few studies attempt to inspect the ovary directly, or indirectly (as with ultrasound). It is clear that the oligomenorrhoeic, obese, hirsute, 'Stein-Leventhal' woman is at the severe end of a spectrum of disease, which probably has more than one aetiology. It is our experience (unpublished observations) that many women with congenital adrenal hyperplasia also have PCO, even though most of the excess androgen is adrenal in origin, and that the polycystic appearance of the ovary persists even after androgen levels have normalized with adequate corticosteroid replacement. Women given androgens before gender-reassignment surgery also have polycystic changes in their ovaries (Amirikia *et al.* 1986). Many of the patients in this study with PCO have a family history of hirsutism, oligomenorrhoea or subfertility. This has been noticed by other workers (Polson *et al.* 1988; Hague *et al.* 1986). It is possible that some cases of PCO may be inherited as a genetic disorder, or may result from exposure of the fetal ovary to excess androgen. Yen (1980) has suggested that obesity at the time of puberty may be a factor involved in the aetiology of the PCO.

In our series hirsuties and oligomenorrhoea were strongly associated with obesity and a high FAI. We have also shown that the FAI is correlated with BMI in normal women as well as in those with PCO, but, as shown in Fig. 2, this rate of rise is much steeper in the women with PCO. The PCO may be considered to be a multifactorial, weight-dependent, androgen-secreting lesion. Weight control is an important aspect of the management of obese, infertile women (Pasquali *et al.* 1986; Bates & Whitworth 1982) and we encourage our patients to maintain their BMI around 21 kg/m^2.

Of our women with oligomenorrhoea 76% had laparoscopic evidence of PCO and all these women had a FAI> 4·5. These results are similar to those reported by Adams *et al.* (1986) who found that 87% of a group with oligomenorrhoea had ultrasound and endocrine evidence of PCO and fewer than half of these patients were hirsute. The FAI is a convenient marker for PCO, especially in a group with oligomenorrhoea (Eden *et al.* 1988*a*; Eden 1988). The other

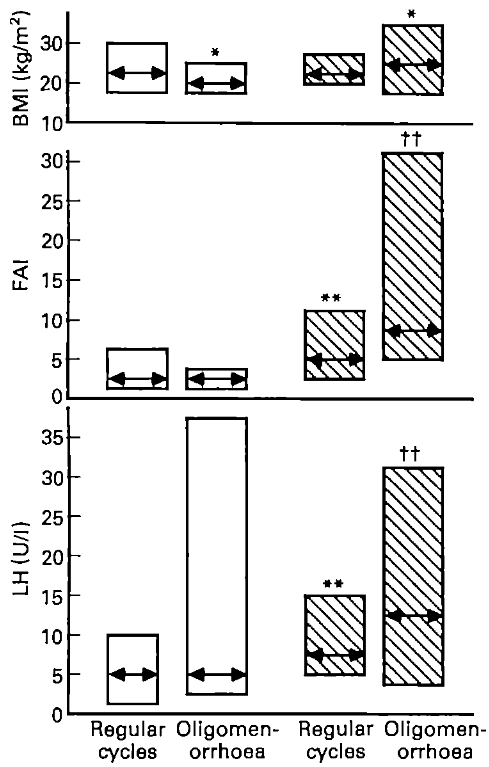

Fig. 1. Results in the four patient categories, expressed as medians (⟷) and ranges (boxes). □, Patients with normal ovaries; ▨, patients with polycystic ovaries (PCO). As in Table 2, each column is compared with the preceding result, except for those patients with PCO and regular cycles who are compared with subjects having normal ovaries and regular cycles ($^{*}P<0{\cdot}05$, $^{**}P<0{\cdot}005$, $^{\dagger\dagger}P<0{\cdot}001$). The large range for oligomenorrhoeic patients with normal ovaries is due to two patients with gonadal failure (Table 1).

causes of oligomenorrhoea are associated with hypogonadism resulting in a significant fall in serum T (Table 2) which may negate the tendency of SHBG to fall because of oestrogen lack. We believe this explains why the FAI is so discriminatory in a group with oligomenorrhoea. In our series of oligomenorrhoeic women, a FAI> 4·5 was 100% specific and sensitive for the presence of PCO. However, an elevated FAI may be found in women with adrenal hyperplasia or an androgen-secreting tumour and these two conditions should be considered in the differential diagnosis of the woman with a markedly elevated FAI. In our infertility clinic, a LH> 10 U/l, T> 2·6 nmol/l, SHBG< 31 nmol DHT/l and a FAI> 4·5 are all acceptably specific to diagnose PCO (Table 3), but overall the FAI is the most sensitive test (82%).

LH and FSH are significantly correlated, both in normal women and those with PCO, which in part explains the poor specificity and sensitivity of the LH/FSH ratio for PCO. It is important to sample patients in the early follicular phase whenever possible, to avoid false-positive results for T and the FAI (especially midcycle) and avoid the potential confusion of the LH surge (Eden *et al.* 1988*b*). The severely obese woman (BMI> 30 $\mathrm{kg/m^2}$) may also have a FAI> 4·5 and low serum levels of SHBG despite having normal ovaries (Eden *et al.* 1988*b*). The FAI appears to fall with age in women with normal ovaries, perhaps reflecting decreasing ovarian androgen production.

Sixteen ovulatory patients (as confirmed by serial scans) had PCO and had no other apparent factor found to explain their subfertility. The significance of this finding is contentious, but it is known that women with PCO can ovulate since a corpus luteum is often found in wedge resections of polycystic ovaries (Goldzieher & Green 1962). In our study, ovulatory women with PCO had significantly higher follicular phase levels of LH and a higher median FAI than those patients

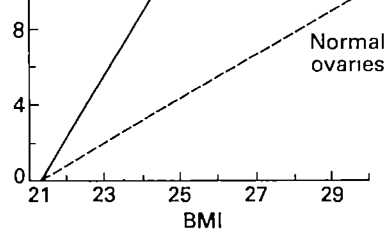

Fig. 2. Relation between free androgen index (FAI) and body-mass index (BMI) expressed as $\mathrm{kg/m^2}$ in women with polycystic ovaries (PCO) and normal ovaries. ———, The linear regression equation for the patients with PCO (FAI = 21+0·30×BMI, $r = 0{\cdot}41$, $P<0{\cdot}001$); – – –, the linear regression equation for patients with normal ovaries (FAI = 21+0·85×BMI, $r = 0{\cdot}34$, $P<0{\cdot}01$).

Table 3. The discriminatory ability of the tests for PCO

	Sensitivity (%)	Specificity (%)
LH/FSH>3	50	93
LH/FSH>2	87	75
LH>10 U/l*	53	99
SHBG<31 nmol DHT/l	34	100
T>2·6 nmol/l	38	100
FAI>4·5	82	97
Abnormal LH, SHGB, T or FAI	93	93
Ultrasound	97	100

* Excluding patients with gonadal failure (high FSH).

with normal ovaries and regular cycles. Evidence is now emerging that a high follicular phase level of LH is associated with poor rates of in-vitro fertilization (IVF) (Stranger & Yovich 1985; Howles *et al.* 1986), perhaps because of premature activation of the oocyte (Jacobs 1987). Rutherford *et al.* (1988) recently demonstrated an improved success rate for IVF using a regimen involving a LH releasing hormone analogue (buserelin) and human menopausal gonadotrophin (hMG) when compared with clomiphene and hMG therapy. The PCO is also associated with an increased risk of early pregnancy loss (Homberg *et al.* 1988) and recurrent miscarriage (Sagle *et al.* 1988). It is also possible that excess androgen production may impair intrafollicular function (Yen 1980).

This study supports the hypothesis that the PCO is common (Polson *et al.* 1988) and confirms the observation that a visual diagnosis of PCO (ultrasound or laparoscopy) is usually supported by hormonal evidence of hyperandrogenicity or an elevated follicular phase level of LH (Adams *et al.* 1986). It is suggested that these endocrine abnormalities may contribute to the infertility associated with the PCO.

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Bladder neck electrical conductivity in female urinary urgency and urge incontinence

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Summary. Thirty-nine consecutive women, referred because of lower urinary tract symptoms of stress incontinence, urgency and urge incontinence, were interviewed and their symptoms were graded using a standardized questionnaire. They were investigated with conventional, fast-fill cystometry and with a new bladder neck electrical conductivity (BNEC) test which measures bladder neck activity. A highly significant correlation between the symptoms of urgency and urge incontinence and the maximum amplitude of bladder neck activity was found with the new test. The correlation of the maximum deflection at rest with the symptom of urgency was significantly better than the best correlation found with the cystometric measurements. The values for sensitivity and specificity of cystometry for the detection of an abnormality associated with urgency were 58% and 92% respectively, and the corresponding values for a positive BNEC test (as defined by a maximum deflection at rest >13 μA) were 100% and 77%.

Cystometry is the most widely accepted test of lower urinary tract function. It has the benefit of theoretical acceptability and tradition. Intuitively it is seen that the higher the pressure within the bladder, the greater the propensity for urine to leak. Cystometry was described over 100 years ago (Mosso & Pellacani 1882) and, although the technique has changed, the principles remain the same.

Two abnormalities have been defined using the results obtained during cystometry (Bates *et al.* 1981). (i) Genuine stress incontinence: involuntary loss of urine (from the urethra) when the intravesical pressure exceeds the maximum urethral pressure, but in the absence of detrusor activity. (ii) Detrusor instability (Bates *et al.* 1970): the presence of spontaneous or provoked detrusor contractions during the filling phase, whilst the patient is attempting to inhibit micturition.

Defining an abnormality on the basis of a test, artificially ensures that the test is both diagnostic and highly specific for that condition. Since the results are expressed in terms of continuous variables, it is assumed that cystometry can be used to grade the severity of the condition. Unfortunately, the symptoms of detrusor instability (frequency, nocturia, urgency, urge incontinence and stress incontinence) and their response to treatment correlate poorly with the results of the test (Holmes *et al.* 1983). Indeed, up to 70% of patients with stable cystometrograms complain of the symptom of urgency (Abrams 1983) and 55% complain of urge incon-

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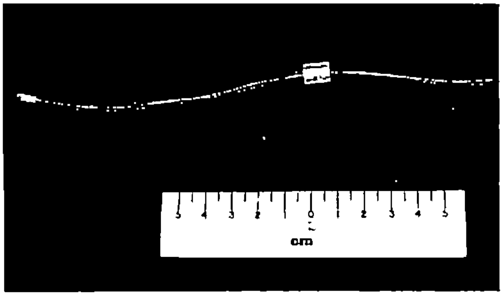

Fig. 1. Conductivity catheter illustrating the catheter fixation device which stabilizes the electrodes at a fixed distance from the external urethral meatus The suture provides sufficient friction to stabilize the collar during use but allows it to slide into position with ease. The device is held between the labia minora at the external urethral meatus.

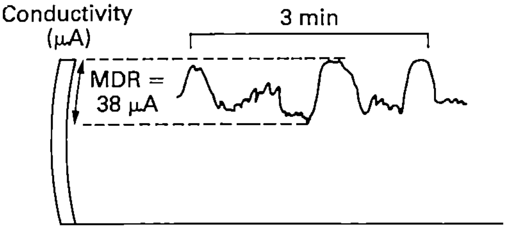

Fig. 2. The method of deriving the maximum deflection at rest (MDR) during a bladder neck electrical conductivity (BNEC) test.

tinence (Cantor & Bates 1980). In a group of 75 women who complained of urgency, 36 had objectively stable bladders at cystometry (Jarvis *et al.* 1980).

Conventional cystometry detects involuntary detrusor contractions and is a specific test for detrusor instability. Since detrusor instability cannot reliably be distinguished symptomatically from 'sensory urgency', cystometry is an insensitive test for abnormalities associated with urgency and urge incontinence.

Urgency has been described as the cardinal bladder symptom (McGuire 1985), but little is known about its mechanism (Powell & Feneley 1980). Initial work has indicated that the electrical field effect around two ring electrodes, when a high frequency AC voltage is applied between them, may be used to monitor the activity of the bladder neck mechanism and has shown that this is closely associated with the symptom of urgency (Holmes 1987); bladder neck activity can occur not only with unstable contractions, but also in their absence.

The purpose of this study was to investigate whether the magnitude of the bladder neck electrical conductivity (BNEC) variation (which is an objective estimate of the activity of the bladder neck) correlated with a subjective assessment of the severity of the symptoms of urgency and urge incontinence. The same women were also investigated with conventional fast-fill twin-channel cystometry and the correlation between the cystometric variables and the severity of the symptoms was compared with the BNEC correlation.

Subjects and methods

During 1 month, 39 consecutive, neurologically normal women undergoing investigation of their lower urinary tract were enrolled in this study. A detailed urodynamic history and examination was performed using a standardized questionnaire (Cardozo *et al.* 1978). The symptoms of urgency, urge incontinence and stress incontinence were graded subjectively as 0=absent, 1=occasionally a problem, or 2=frequently a problem. The age of each woman was also recorded.

After the urinary flow rate was measured, the women were catheterized to drain residual urine and had 250 ml of 0·9% saline at room temperature instilled into the bladder; the catheter was then removed. The electrodes of a conductivity catheter (Fig. 1) were then placed at the bladder neck mechanism with the woman lying comfortably in the supine position. The catheter was held at this point for 3 min with the fixation device. Any patient movement or catheter readjustment was marked on the chart. The catheter was then removed and fast-fill twin-channel cystometry performed. The volume at which the first desire to void occurred and the maximum pressure rise (in cm H_2O) during the filling phase

Table 1. Subjective assessment of symptoms of urgency by grade of severity in 39 women in the study

	Grade of severity*		
Symptom	0	1	2
Stress incontinence	14	14	11
Urgency	13	8	18
Urge incontinence	22	7	10

* Symptoms of urgency were graded as 0 = absent, 1 = occasionally a problem, 2 = frequently a problem.

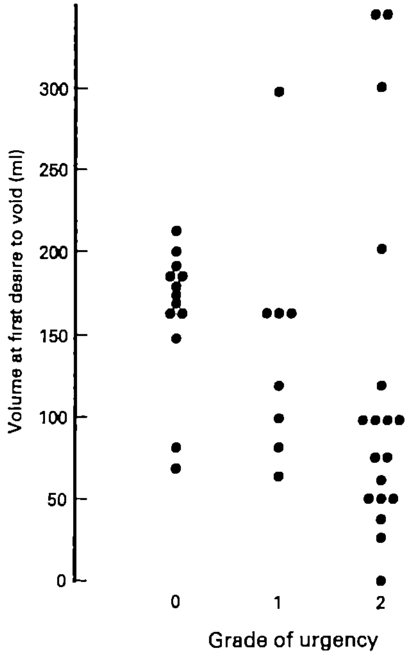

Fig. 3.

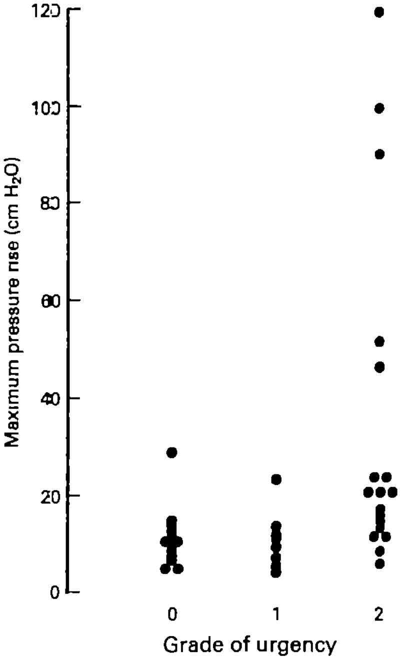

Fig. 4.

Figs 3 & 4. Correlation between subjective symptoms of urgency (graded as 0=absent, 1=occasionally a problem, 2=frequently a problem) and volume at first desire to void (Fig. 3) or maximum pressure rise during cystometry (Fig. 4).

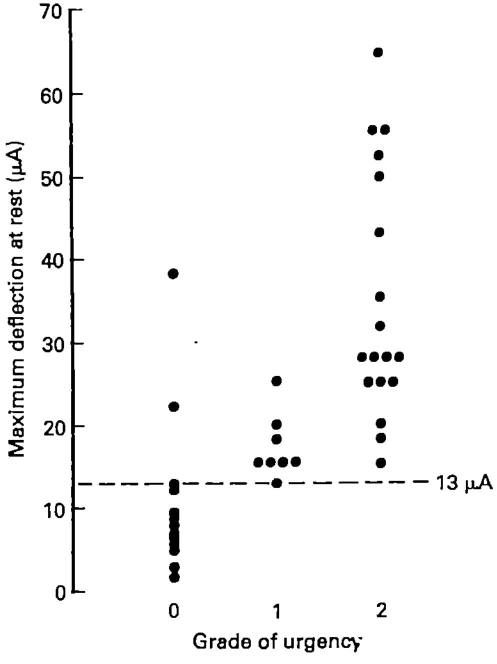

Fig. 5. Correlation between subjective grade of urgency and maximum deflection of conductivity at rest.

were recorded. The conductivity charts were then analysed by measuring the maximum deflection at rest (in μA) from peak to trough seen over the course of the 3 min (Fig. 2).

The relation between conventional cystometry, the BNEC measurement and the patient's subjective symptoms was assessed using Kendall's rank correlation coefficient.

To exclude a degenerative effect, the association of the symptoms with age was also investigated.

Results

All tracings were suitable for analysis. The mean age of the 39 women in the study was 44·3 years (range 25–68 years). Of these 39 women 13 denied urgency or urge incontinence and these acted as a comparison group. Table 1 details the subjective symptoms by grade of severity (0–2) in the 39 women.

The volume at which the first desire to void occurred, the maximum pressure rise (cm H_2O) and the maximum deflection at rest (μA) found

Table 2. Summary of the statistical analysis of the data obtained in 39 women

	Subjective severity of					
	Urgency		Urge incontinence		Stress incontinence	
	τ_B	P	τ_B	P	τ_B	P
Age	−0·26	<0·05	−0·12	>0·05	0·34	<0·05
Volume at first desire to void	−0·35	<0·01	−0·19	>0·05	0·27	<0·05
Maximum pressure rise at cystometry	0·36	<0·01	0·28	<0·01	−0·07	>0·05
Maximum deflection of conductivity trace at rest	0·68	<0·0001	0·49	<0·005	−0·14	>0·05

during the conductivity studies were plotted against the subjective grade of symptoms (Figs 3–5). Kendall's rank correlation coefficient τ_B was calculated for each and assessed for statistical significance; the results are summarized in Table 2. Eleven women with urgency had a positive BNEC test (maximum deflection at rest >13μA) but had stable cystometrograms. No women with detrusor instability had a negative BNEC test. This is statistically significant using McNemar's test (P<0·001).

Discussion

Any new test must be considered in terms of its sensitivity and specificity when compared with established tests. A maximum deflection at rest of >13 μA during the BNEC test was taken as positive to preclude any false-negative results, since it appeared that deflections greater than this were associated with the presence of urgency. A positive cystometry result was defined by the occurrence of involuntary detrusor activity during provocative cystometry. The presence of any symptom of urgency was taken as positive. These results are illustrated in a Venn diagram (Fig. 6).

The sensitivity and specificity of each test are shown in Table 3. The true sensitivity and specificity of the BNEC testing can only be determined once the normal range of the maximum deflection at rest has been established by investigating a large number of women. BNEC testing provides a highly useful test for detecting an abnormality closely associated with urinary urgency and urge incontinence. Of the three women who had a positive BNEC test but who denied the symptom of urgency in general, one experienced urgency during the test. She also denied incontinence but had a urine leakage of more than 2 g with the 1-h ICS pad test (Bates *et al.* 1983), and the cystometry findings revealed genuine stress incontinence. The 58% sensitivity and 92% specificity of cystometry in our series are similar to the corresponding values of 52% and 88% reported by Jarvis *et al.* (1980).

The highly significant correlation between the severity of symptoms combined with high diagnostic power implies that BNEC testing is not only a diagnostic test for an abnormality closely associated with urgency, but may also be used as a predictive test. This means that it could be used to monitor the course of the condition and its response to treatment.

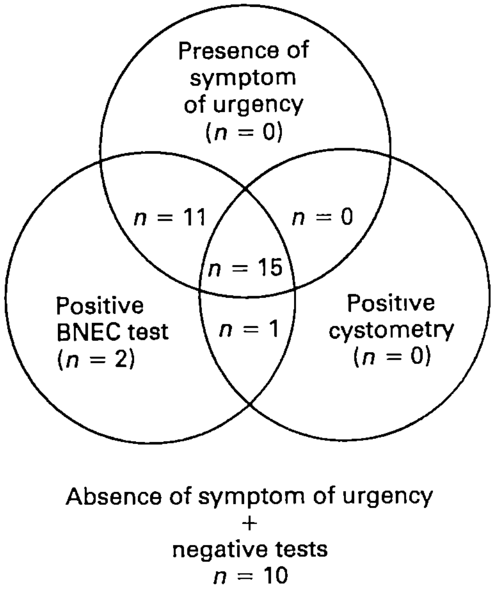
Presence of symptom of urgency (n = 0)
n = 11
n = 0
n = 15
Positive BNEC test (n = 2)
n = 1
Positive cystometry (n = 0)
Absence of symptom of urgency + negative tests n = 10

Fig. 6. Venn diagram to illustrate the combinations of the presence of urgency with the cystometry and conductivity test results in 39 women.

Table 3. Detection of abnormalities associated with symptoms of urgency by means of cystometry or by bladder neck electrical conductivity (BNEC) tests

Test	Urgency		
	Present	Absent	Total
Cystometry			
Positive (detrusor instability)	15	1	16
Negative (stable bladder)	11	12	23
Total	26	13	39
BNEC measurement			
Positive (>13 μA)	26	3	29
Negative	0	10	10
Total	26	13	39

Cystometry: sensitivity = 15/26 = 58%; specificity = 12/13 = 92%.

BNEC test: sensitivity = 26/26 = 100%; specificity = 10/13 = 77%

The correlation of the symptoms of urgency with age in our study contrasts with findings reported by Bungay *et al.* (1980) but the age distribution of their large unselected study population was different from that of our study group, and thus no valid comparison can be made. The women in our study were referred because of the severity of their symptoms, young women with severe symptoms being referred more frequently than older women with comparable symptoms.

Acknowledgments

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Bladder neck electrical conductivity in the treatment of detrusor instability with biofeedback

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Summary. A new method for controlling the symptoms and objective signs of detrusor instability was investigated in a pilot study. The method uses the activity of the bladder neck, monitored by a conductivity catheter, as a biofeedback signal. Voluntary closure of the bladder neck mechanism abolishes abnormal detrusor activity. Ten severely symptomatic women with detrusor instability were assessed clinically and urodynamically before and after a course of biofeedback. Statistically significant improvements in the symptoms of urgency and urge incontinence were found. Five of the seven women who agreed to have repeat cystometry had stable cystometrograms. There was a statistically significant fall in the mean maximum deflection at rest from 41·5 to 16·5 μA ($P<0·05$) measured during bladder neck electrical conductivity tests before and after treatment.

The plethora of treatments for detrusor instability indicates our inadequate understanding of its aetiology and pathogenesis and this is reflected by our low treatment success rate. Bladder retraining and drugs remain the mainstays of management. The former is difficult to supervise and the efficacy of drugs is often limited by side-effects.

A method of treating detrusor instability by displaying detrusor pressure during filling cystometry has been described by Cardozo *et al.* (1978*a*, *b*). In their series of 27 women, 22 reported initial symptomatic improvement and 16 showed objective urodynamic improvement, an improvement rate of 81% using subjective and objective criteria. The subjective improvement was maintained by 4 of 11 women at the 5-year follow-up. These results are similar to the initial cure rates of 84% quoted for bladder retraining in the treatment of detrusor instability (Frewen 1978; Jarvis 1981) and 73% for bladder discipline in treating urge incontinence (Jeffcoate & Francis 1966). The improvement rate of 36% at 5 years for a biofeedback treatment (Cardozo & Stanton 1985) is similar to the rate of 48% reported at the 3-year follow-up by Holmes *et al.* (1983) for bladder retraining in women with urge incontinence.

Biofeedback was not, however, successful in those women with detrusor pressure rises of >60 cm H_2O and functional bladder capacities of <200 ml.

Holmes *et al.* (1989) described a method of monitoring the activity of the bladder neck mechanism with a conductivity catheter. Changes in conductivity at the bladder neck mechanism are consistently seen to precede

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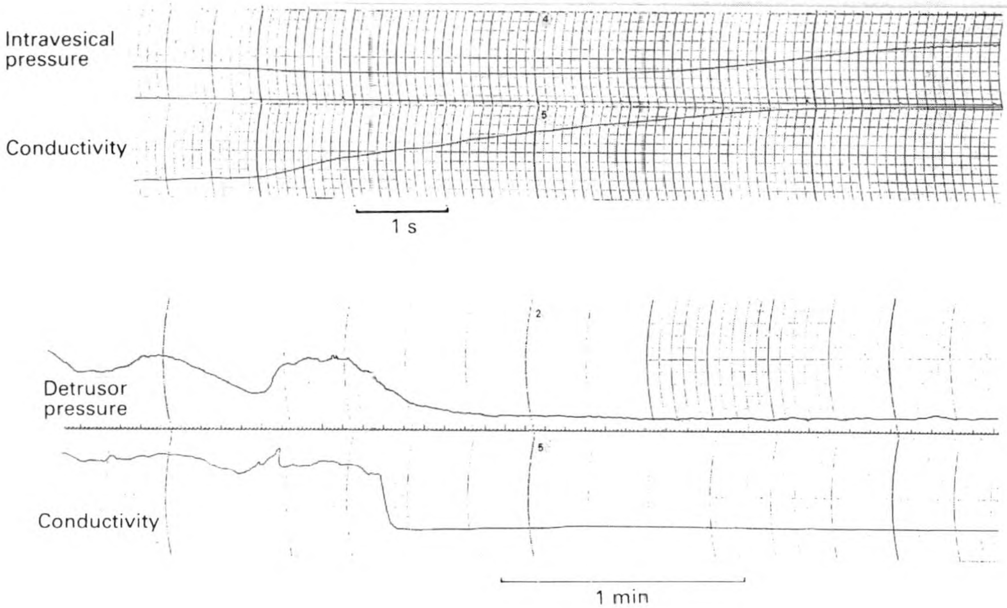

Figs 1 & 2. Simultaneously measured detrusor pressure and bladder neck conductivity in a woman who had involuntary detrusor contractions with 250 ml of 0·9% saline in her bladder. (1) In upper figure note that the conductivity increase precedes the increase in pressure by 3–4 s. (2) In lower figure note that gaining control of the conductivity trace precedes the disappearance of the involuntary detrusor pressure rises.

changes in detrusor pressure when the bladder contains 250 ml of 0·9% saline. The time lag between a rise in conductivity and any detectable detrusor pressure rise has been measured as 4 s (Fig. 1).

Voluntary closure of the bladder neck mechanism (as evidenced by a decrease in conductivity) abolishes abnormal detrusor pressure rises (Fig. 2) and reduces the subjective sensation of urgency.

To test the hypothesis that bladder neck electrical conductivity (BNEC) is likely to be effective as a biofeedback signal, a selected group of women with severe, symptomatic detrusor instability were enrolled in a study to treat their symptoms of urgency and urge incontinence.

Subjects and methods

Ten women with severe, symptomatic detrusor instability were selected because of their failure to respond to, or dislike of, conventional treatment. Eight had already failed to respond to previous anti-cholinergic therapy or psychological treatment, but none was being actively treated at the time of study. All were neurologically normal and had no previous bladder neck surgery. Those whose functional capacity

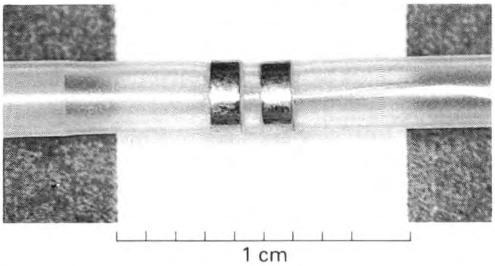

Fig. 3. The electrodes of a urethral electrical conductance (UEC) catheter.

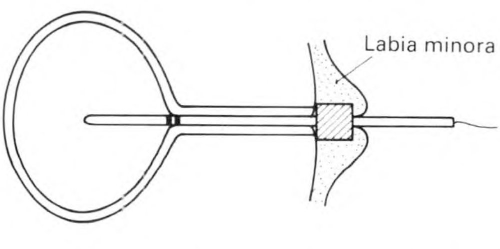

Fig. 4. Diagram to illustrate the position of the UEC electrodes during biofeedback sessions.

Table 1. Comparison of subjective symptoms of urgency before and after biofeedback treatment in 10 women with detrusor instability using BNEC as the biofeedback signal

Symptom grade*	Number of women with symptoms Before biofeedback	 After biofeedback
Urgency		
0	0	2
1	0	6
2	10	2
Urge incontinence		
0	1	6
1	3	2
2	6	2

* Symptoms were graded as 0 = absent, 1 = occasionally a problem, 2 = frequently a problem.

was <400 ml had been cystoscoped under general anaesthesia to confirm normal bladder capacity. Current urinary tract infections were excluded.

During the initial assessment session, the women were catheterized with both a filling catheter and a 4F paediatric feeding tube which was used to monitor intravesical pressure. The bladder was then filled with 0·9% saline at room temperature at a rate of 100 ml/min. Filling was stopped when either an involuntary contraction occurred, or a volume of 250 ml had been instilled. The filling catheter was then withdrawn, leaving the pressure monitoring catheter in position. A conductivity catheter was then inserted and the electrodes (Fig. 3) left at the bladder neck mechanism to record a BNEC test (Holmes *et al.* 1989) (Fig. 4). The women were shown the tracings of both conductivity and intravesical pressure in a mirror, so that they could remain comfortably in the dorsal position whilst observing the chart. They were encouraged to try to control the conductivity tracing, and the association between increases in the sensation of urgency and increases in the conductivity was pointed out. The relation between changes in conductivity and involuntary detrusor pressure rises was also demonstrated in those who generated involuntary detrusor contractions during the investigation. They were then encouraged to maintain the conductivity tracing at a low value for the rest of the session. The conductivity catheter was then removed, the patient voided in private, and was shown the volume of urine which she had contained in her bladder.

At all subsequent sessions, the women were catheterized and a specimen of urine sent for bacteriological culture. Their bladders were filled with 250 ml of 0·9% saline. All were able to tolerate this volume without difficulty by concentrating on the mental picture they had developed of decreasing the BNEC during bladder filling. The filling catheter was removed and the conductivity catheter inserted. The catheter was positioned at the bladder neck mechanism and

Table 2. Comparison of urodynamic findings before and after biofeedback treatment in 10 women with detrusor instability using BNEC as the biofeedback signal

	Before treatment		After treatment		Wilcoxon matched-pairs signed-rank test			
	Mean	Range	Mean	Range	N	T_1	T_2	P
Maximum pressure rise during cystometry (cm H_2O)	62·9	(24–119)	16·3	(0–50)	7	27	1	<0·05
Volume at first desire to void (ml)	81·0	(30–160)	133·0	(80–220)	10	0	36	<0·01
Maximum bladder neck conductivity variation at rest (μA)	41·5	(21–82·5)	16·5	(7–41)	10	55	0	<0·01
Volume at first unstable contraction (ml)	164	(30–440)	320	(200–440)	2	—	—	—
Number with cystometrically diagnosed detrusor instability	10/10		2/7		McNemar's test (7/7 *vs* 2/7) $P = 0·06$			

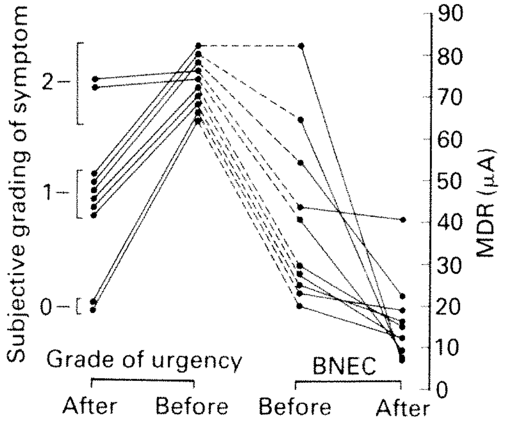

Fig. 5. Subjective grade of urgency and the corresponding bladder neck electrical conductivity (BNEC) test results before and after a course of biofeedback in 10 women. MDR, Maximum deflection at rest.

the tracing was shown to the woman who was asked to concentrate on keeping the conductivity trace at as low a value as possible for the rest of the session. During the biofeedback sessions, the women were left alone in the laboratory to prevent distraction, but knew that help and advice were available in the adjacent room should it be required. Occasionally the catheter required readjustment during the session to make control of the tracing more or less difficult. Movement of the catheter inwards made control of the conductivity more difficult, whilst moving it outwards made it less difficult.

Between sessions the women were encouraged to spend an unspecified time each day repeating the exercise without catheterization. They developed a mental picture of the association between their physical actions and decreasing the conductivity at the bladder neck mechanism.

Sessions were continued until either the patient found she was no longer subjectively improving, or that eight sessions had been completed with no significant subjective improvement. The patient then had a repeat BNEC test and fast-fill cystometry.

The pre- and post-treatment symptom assessment and urodynamic data were compared using Wilcoxon matched-pairs signed-rank test and McNemar's test as appropriate.

Results

The mean age of the women was 34·8 years (range 25–53 years). The mean length of the time symptoms had been present was 18·5 years (range 0·5–41 years). Eight had functional bladder capacities of <200 ml and four had detrusor pressure rises of >60 cm water. All women preferred the BNEC test to cystometry.

No urinary tract infections were detected during the study. Each session lasted at least 30 min and the mean number of sessions was 5·4 (range 3–8). The symptoms before and after biofeedback are summarized in Table 1. The subjective improvements were statistically significant (urgency $P<0{\cdot}01$, urge incontinence $P<0{\cdot}01$).

Urodynamic data were not available for one woman because after eight sessions of biofeedback she felt that her symptoms were unchanged and had restarted oxybutinin before reinvestigation, which was then felt to be unethical. Her cystometric data were omitted from the statistical analysis, but the last BNEC test results obtained before she restarted oxybutinin are included.

Two women were not prepared to have repeat cystometry, but did allow repeat BNEC testing. The volume at which the first desire to void occurred was recorded during bladder filling for this test. The urodynamic findings are summarized in Table 2, and the data pertaining to the symptom of urgency in Fig. 5.

BNEC tests before and after biofeedback treatment in one woman are illustrated in Fig. 6.

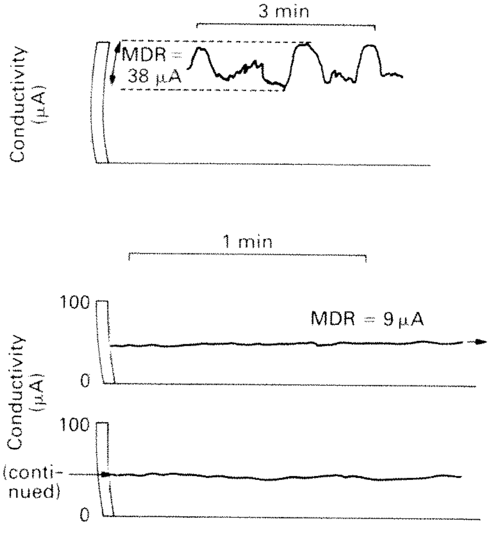

Fig. 6. Bladder neck electrical conductivity (BNEC) test [measuring the maximum deflection at rest (MDR)] before (upper) and after (lower) biofeedback treatment.

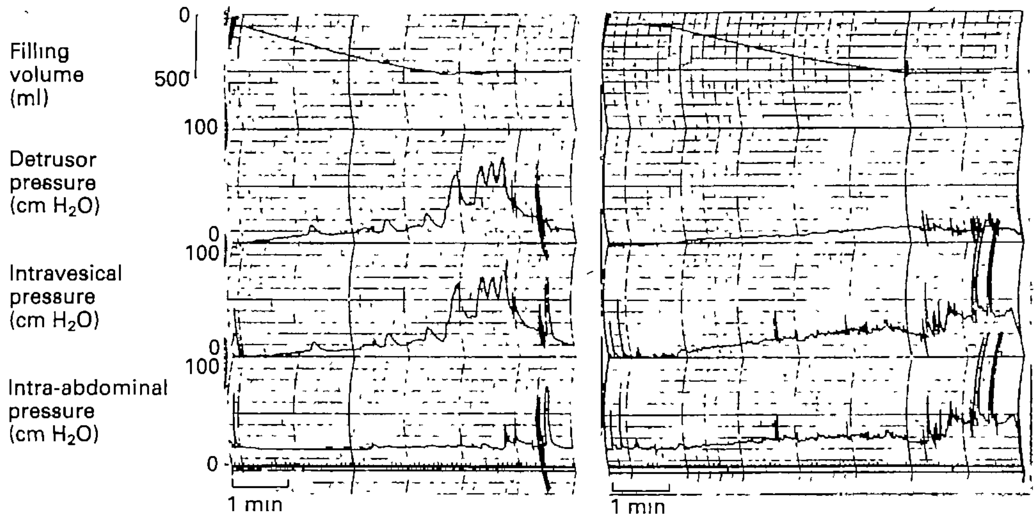

Fig. 7. Cystometry tracings before (left) and after (right) biofeedback treatment in the same woman shown in Fig 6.

Her cystometry tracings obtained before and after biofeedback treatment are illustrated in Fig. 7.

Eight of the 10 women had significant improvement in their symptoms of urgency, whilst four of the six who complained of severe urge incontinence subjectively improved after treatment. Only two had objective evidence of detrusor instability after treatment. There was a significant fall in the mean maximum deflection at rest from 41·5 μA (range 21–82·5) to 16·5 μA (range 7–41).

Two of the four women with initial detrusor pressure rises of more than 60 cm H_2O had repeat cystometry. Both had stable bladders. Five of the eight women whose functional capacities were <200 ml converted to stability.

Discussion

This was an uncontrolled pilot study and the results cannot be extrapolated to all women with idiopathic detrusor instability. It does show that over the treatment period there were significant changes in the symptoms and objective assessment of detrusor instability in a group of women who should have been resistant to conventional biofeedback treatment using detrusor pressure as the biofeedback signal. Any treatment of detrusor instability is recognized to have a placebo effect, but since both subjective and objective improvements have been demonstrated, it is unlikely that this was the only mechanism (Katkin & Goldband 1979).

The bladder neck seems to open before any detectable detrusor pressure rise and its closure precedes a fall in detrusor pressure. The inference of this observation is that bladder neck opening is a separate, earlier event in the genesis of a detrusor contraction which would account for its improved efficacy as a biofeedback signal when compared with detrusor pressure.

Acknowledgments

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Perinatal mortality in rural Tanzania

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Summary. Prolonged labour was the most frequent cause of perinatal death in a rural hospital in the south western highlands of Tanzania. After the introduction of an obstetric policy aiming to prevent prolonged labour by making use of the guidelines of the partogram, perinatal mortality was reduced from 71 to 39 per 1000 births. Baird's clinico-pathological classification is still considered a useful instrument for the discovery of avoidable factors in perinatal deaths. The concept of the partogram should be an integral part of the training of medical auxiliaries in the field of maternal and child health (MCH).

Perinatal mortality is related to maternal health and physique, as well as to the standards of obstetric care (Baird 1969). Both are associated with the overall socio-economic circumstances, but intrauterine life seems to be better protected against adverse effects than is extrauterine life: in the Third World perinatal mortality is eight times, infant mortality 20 times and under-five mortality 45 times higher than in the Western World (Sikkel 1983). A high literacy rate has been shown to be associated with a lower perinatal mortality rate in Nigeria (Harrison 1985). Further development of the rural areas and elimination of poverty, ignorance and disease eventually leads to reduced perinatal mortality rates.

Nevertheless, perinatal mortality is still the best available index of obstetric care (Chalmers 1980), especially where rates are high as in most African countries. Standards of obstetric care can be assessed by surveying perinatal deaths. Most published reports on perinatal mortality in African countries stem from large urban teaching hospitals (Dawodu *et al.* 1984; Harrison 1985; Versluys & Casson 1975). The only known population-based study in rural Africa is from Machakos in Kenya, where a surprisingly low perinatal mortality rate of 46 per 1000 births was found in 1975–1978 (Voorhoeve *et al.* 1984). The stillbirth rate in hospital was almost twice the rate found in home deliveries, while the early neonatal death rate was almost the same at home as in hospital.

It is difficult to compare rates in different hospitals because of differences in patient selection and referral. Comparison of perinatal mortality rates at different periods in the same hospital, however, may give an indication of mortality trends and, within certain limits, these may be used to assess different policies of obstetric management in that hospital.

In this article, data are presented on perinatal mortality in a rural hospital in the south western highlands of Tanzania during the period 1971 to 1979. Experience during the earlier part of this period suggested that a considerable number of perinatal deaths could be prevented easily by the use of quite limited resources. New policies were introduced and these proved effective in reducing the perinatal mortality rate.

Patients and methods

All case-records of stillborn infants (with a birthweight of ≥1000 g) in Lugarawa hospital from September 1971 to September 1976 were analysed retrospectively for avoidable factors leading to death: 137 case-records were included in

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the study, giving a stillbirth rate of 48 per 1000 in 2875 births.

Lugarawa hospital was the only hospital in Ludewa district in the south western highlands of Tanzania. The district contained about 75 000 inhabitants in 1978 and with a birth rate of 45 per 1000 it could be calculated that 24% of all pregnant women were delivered in Lugarawa hospital annually. Maternal health services were provided by medical auxiliaries, supervised by a general doctor. Transport in the district was very unreliable.

Avoidable factors, related to the performance of health workers, could be classified into four categories: (1) Delay in referral from health centres and dispensaries This can be due to failure to identify high-risk pregnancies or to faulty patient management leading to a late referral. (2) Delay in the first stage of labour in hospital without appropriate action. (3) Delay in the second stage of labour in hospital without appropriate action. (4) Fetal distress during labour in hospital without appropriate action.

As the analysis of stillbirths provided enough suggestions for the improvement of obstetric care, analysis of early neonatal deaths with regard to avoidable factors was not deemed necessary. It was assumed that apart from deaths due to immaturity (also related to infection) and congenital anomalies, the associations with early neonatal deaths would be similar to those for stillbirths.

After analysis of the period 1971–1976, changes were introduced in the obstetric policies of the hospital during the period between 1 September 1976 and 1 January 1977.

A detailed comparison was made of perinatal mortality in the following two periods in Lugarawa hospital: 1 September 1971 to 1 January 1977, in which there were 3102 births to 3054 women (the period before and during the introduction of the new policy), and 1 January 1977 to 1 May 1979, in which there were 1959 births to 1929 women (the period after the introduction). There were no differences in record-keeping between the two periods

Routine management of labour was altered in the following ways. When labour reached the active phase (defined as a cervical dilatation of 4 cm, effacement of the cervix and regular contractions (Studd 1975)) and the vertex was engaged (to reduce the risk of cord prolapse), membranes were artificially ruptured in order to shorten the length of labour (O'Driscoll & Stronge 1975; Stewart *et al.* 1982). In cases of first-stage delay, labour was augmented with intravenous oxytocin in order to differentiate cephalopelvic disproportion from uterine inertia. In the absence of fetal distress, instrumental delivery was indicated in the second stage of labour, when this lasted more than 60 min in primigravidae and more than 30 min in multigravidae. More attention was devoted to the detection of fetal distress, mainly by more frequent listening to the fetal heart: during the first stage every 15 to 30 min and in the second stage of labour after every contraction. A perinatal mortality review meeting was instituted for all members of the hospital staff every 3 months. All perinatal deaths in the preceding period were discussed openly in order to learn from the errors made.

While the above changes concerned management in hospital, the following was applicable to obstetric care in the district. Consultations with the rural health workers in dispensaries and health centres were started with the aim of increasing their knowledge of antenatal risk factors. Antenatal clinics were supervised in order to improve the process of identifying high-risk pregnancies.

The guidelines described by Philpott & Castle (1972), who developed the partogram, were followed. Labour was augmented with oxytocin when the partogram crossed the 'action' line, which was drawn parallel to the 'alert' line, but (arbitrarily) 4 h to the right. When labour was supervised in a dispensary or a health centre, the period between the alert and action line was used to indicate the need for referral to hospital.

The change in policy influenced obstetric intervention so that there was a significant increase in augmentation with oxytocin, symphyseotomy and vacuum extraction in the period 1977–1979 (Table 1).

Results

Avoidable factors in 137 stillbirths (1971–1976)

The most frequent causes of stillbirths, diagnosed on clinico-pathological grounds (Barron & Thomson 1983), were classified as mechanical (55%), among which obstructed labour (38%) ranked first. As most infants dying during obstructed labour had birthweights of ≥2500 g (85%), prevention and early management of

Table 1. Obstetric interventions, complications and outcome in Lugarawa hospital, Tanzania

	1971–1976	1977–1979
Total no. of women	3054	1929
Obstetric interventions		
Augmentation with oxytocin*	20 (0·7%)	88 (4·6%)
Vacuum extraction**	146 (4·8%)	143 (7·4%)
Symphyseotomy***	1 (0·03%)	18 (0·9%)
Caesarean section	78 (2·6%)	65 (3·4%)
Destructive operation	4 (0·1%)	3 (0·2%)
Repair of uterine rupture	9 (0·3%)	4 (0·2%)
Obstetric complications		
Multiple pregnancy	46 (1·5%)	30 (1·6%)
Antepartum haemorrhage	25 (0·8%)	12 (0·6%)
Uterine rupture	10 (0·3%)	4 (0·2%)
Pre-eclampsia	3 (0·1%)	3 (0·2%)
Maternal mortality (per 100 000 pregnancies)	11 (360)	6 (311)
Total no. of babies born	3102	1959
Breech presentation	106 (3·4%)	61 (3·1%)
Face and brow presentation	23 (0·8%)	11 (0·6%)
Transverse presentation	20 (0·7%)	11 (0·6%)
Cord prolapse	15 (0·5%)	14 (0·7%)
Birthweight <2500 g	532 (17%)	330 (17%)
Perinatal mortality <2500 g (rate/1000 births)	88/532 (165)	35/330 (106)
Perinatal mortality ≥2500 g (rate/1000 births)	131/2570 (51)	42/1629 (26)
Perinatal mortality all weights**** (rate/1000 births)	219/3102 (71)	77/1959 (39)

* χ^2 85·1; $P<0{\cdot}0001$.
** χ^2 14·9; $P<0{\cdot}001$.
*** χ^2 25·2; $P<0{\cdot}001$
**** χ^2 21·4; $P<0{\cdot}001$.

obstructed labour can lead to a considerable lowering of perinatal mortality.

Avoidable factors were found to be present in 34 of 137 stillbirths (25%). As the analysis was retrospective and based on what had been reported in the medical records, it is likely that there was an underestimation of avoidable factors.

Delay in referral from health centres and dispensaries. In this category (7 stillbirths) the health workers had failed to detect that the woman was 'at risk'. Some women should have been referred to hospital much earlier and certainly before the onset of labour. In others, the decision about the place of birth had been made correctly, but labour was wrongly managed, resulting in delayed referral to hospital during labour.

No appropriate action in a delayed first stage. This was considered to be the cause in seven stillbirths. When studying delay in the first stage of labour, it is often impossible to know accurately when labour started. As a general guideline, progress in cervical dilatation of 1 cm per 1 or 2 h was considered as the lower limit of normal, and delay was diagnosed when progress was less than this (Philpott & Castle 1972).

No appropriate action in a delayed second stage in hospital. The six primigravidae in this category had a mean duration of second-stage labour of 159 min (range 75–450; 60 min was arbitrarily chosen as the upper limit of a normal second stage in the absence of fetal distress). For the eight multigravidae in this category a mean of 112 min was recorded (range 56–180; 30 min as limit).

No appropriate action when fetal distress was diagnosed. This occurred in six stillbirths. The only available means to detect fetal distress were the appearance of meconium-stained amniotic fluid and the auscultation of the fetal heart sounds. Meconium staining was only considered to be a sign of distress when it appeared together with fetal heart rate abnormalities.

In summary, avoidable aspects were present in 25% of stillbirths in hospital, obstructed labour being the most important factor. Most of these stillborn infants had a birthweight of ≥2500 g. In 21% (7/34), deficiencies beyond the responsible hospital indicated a need for change in midwifery policy in the community. In the other 79% (27/34), deficiencies in hospital management were responsible, showing the need for a continuous perinatal audit in hospital (Keirse 1985). On the basis of these findings and after consultations with the hospital staff, obstetric policy in the hospital was changed with the aim of reducing the occurrence of prolonged labour, and thereby perinatal mortality.

Perinatal mortality review during the two periods

After the introduction of the new policy, the perinatal mortality rate was reduced from 71 to 39 per 1000 births (Table 1). The percentage of primigravidae delivered in hospital in 1976 (22%) was similar to that in the second period (22%) Such data were not available for the years 1971–1975, but there are no reasons to assume that there had been much change. Low birthweight occurred in 17% in both periods. The perinatal mortality rate decreased from 165 to 106 in low-birthweight infants and from 51 to 26 in the group of babies with a birthweight of ≥2500 g (Table 1). Data on maternal age are not available as this is not known by many of the women. In both periods approximately two thirds of all deliveries were considered normal (using the same definitions). No difference in the prevalence of some obstetric conditions, which are known to increase perinatal mortality, was found between the two periods under review (Table 1).

Breech delivery. Birthweight-specific perinatal mortality and the distribution of birthweight in breech delivery did not differ significantly between the two periods (Table 1). In 1977 the percentage of fetal deaths in breech deliveries that had occurred before admission (36%) was higher than in the period 1971–1976 (26%). The lowest perinatal mortality rate in breech deliveries was associated with birthweights between 2500 and 2999 g.

Twin delivery. Perinatal mortality in all weight groups was lower in the second than in the first period under review, although the differences were not statistically significant. There was, however, a significant difference in birthweight distribution: 13% of twins had a birthweight below 1500 g in 1971–1976 compared with none in 1977–1979, while the percentage with a birthweight ≥2500 g doubled in the second period. The numbers of other obstetric complications were too small to allow comparison.

Caesarean section. The perinatal mortality rate after caesarean section decreased from 165 to 75, but the difference was not statistically significant (Table 2). The relative frequencies of the different reasons for performing caesarean section did not differ much between the two

Table 2. Perinatal mortality and indications for caesarean section (CS) in Lugarawa hospital

	1971–1976		1977–1979	
Indication for CS	Sections *n* (%)	Perinatal deaths *n* (rate/1000 births)	Sections *n* (%)	Perinatal deaths *n* (rate/1000 births)
Total no. of CS	78		65	
CPD	39 (50)	7 (179)	35 (54)	2 (57)
Repeat CS	12 (15)	0 (0)	15 (23)	0 (0)
Arm prolapse	10 (13)*	1 (91)	9 (14)*	2 (182)
Placenta praevia	8 (10)	4 (500)	3 (5)	1 (333)
Others	9 (12)	1 (111)	3 (5)	0 (0)
Total no. of newborn	79	13 (165)	67	5 (75)**

CPD, Cephalopelvic disproportion.

*Eleven babies were born in this group.

**χ^2 2, 94; $0{\cdot}05<P<0{\cdot}1$.

periods. Although absolute numbers are small, the perinatal mortality rate after caesarean section for cephalopelvic disproportion was reduced from 179 to 57 per 1000 births.

Vacuum extraction. The perinatal mortality rate after vacuum extraction was significantly decreased from 250 to 90. The decision to perform a vacuum extraction was made earlier in labour in the second period of the study; during this period 20% of the extractions were performed in the late first stage whereas in 1971–1976 vacuum extraction was performed only in the second stage of labour. Fetal distress in the late first or early second stage was the indication for 52% of all extractions in the second period compared with 26% in the first period. In both periods the highest perinatal mortality was noted when the indication for vacuum extraction was prolonged second stage in combination with fetal distress. For all vacuum extractions mortality was much lower in the second period.

Cause-specific perinatal deaths

For babies with a birthweight of ≥2500 g, there was a significant reduction in perinatal mortality due to obstructed labour and 'death of unknown origin' in the second period of the study (Table 3). Deaths associated with birth asphyxia after an apparently uncomplicated labour are included in the group of deaths of unknown origin.

Augmentation of labour

The second period of the study showed a significant increase in the use of oxytocin (Table 1). Labour was augmented with oxytocin in 67 of 439 primigravidae (15%) and in 21 of 1490 multigravidae (1%). There were 10 perinatal deaths, which included one fetal death before the administration of oxytocin. Most of these deaths were associated with operative vaginal delivery. Augmentation resulting in spontaneous vaginal delivery or caesarean section had a much lower perinatal mortality. Therefore, mortality seemed to be related more to difficult vaginal delivery than to the use of oxytocin *per se*.

Infants born after symphyseotomy had similar mean Apgar scores at 5 min (9·1) as those born spontaneously (9·3) and much higher than those born by vacuum extraction (7·7). Apgar scores after caesarean section (8·2) have to be considered separately because of the involvement of general anaesthesia.

A serious maternal complication occurred in a multigravid woman who collapsed and died when her labour was augmented because of first-stage delay. Post-mortem extraction of the infant (for cultural reasons) and exploration of the uterine cavity revealed no uterine rupture. A provisional diagnosis of amniotic fluid embolism

Table 3. Cause-specific perinatal deaths with a birthweight ≥2500 g in Lugarawa hospital

	1971–1976 (*n*=2570)	1977–1979 (*n*=1629)
All perinatal deaths (≥2500 g)*	131 (51)	42 (26)
Mechanical causes		
Obstructed labour**	52 (20)	18 (11)
Breech delivery†	10	5
Cord prolapse	11	5
Other causes		
Syphilis	5	0
Congenital anomalies	6	2
Antepartum haemorrhage	3	0
Toxaemia	0	1
Death of uncertain origin***	42 (16)	11 (7)
Miscellaneous	2	0

* χ^2 16·0; $P<0{\cdot}001$.
** χ^2 5·1; $P<0{\cdot}05$
*** χ^2 7·4; $P<0{\cdot}01$.
†Twin delivery included.
Results are number of perinatal deaths (rate/1000 births).

was made. Oxytocin is known to be associated with this condition (Cavanagh *et al.* 1982).

Early referral of women with high-risk pregnancies

Before the rural health workers in the dispensaries had received any education on antenatal risk factors, most referrals were emergency admissions after complications had already arisen. Late referrals could be reduced by supervision, and in the second period of the study 54 women who attended the antenatal clinics in two dispensaries 50 and 70 km from Lugarawa hospital were referred before labour had started.

The main reasons for referral were: a history of perinatal death (39%), small stature (below 150 cm) in primigravidae (13%), a previous caesarean section (11%), grand multiparity (7%), suspected twins (6%) and signs of pre-eclampsia (4%). Four of the 57 babies born in this subgroup died perinatally (70 per 1000). There was one maternal death due to severe infectious hepatitis leading to preterm birth, postpartum haemorrhage and hepatic coma. Maternal height was below 150 cm in 33% of the referral group compared with 19% of all women delivered in hospital. Their high obstetric risk was indicated by the outcome of labour: labour was augmented in 11% compared with 5% in all deliveries; 33% required operative vaginal delivery compared with 8%, and 7% were delivered by caesarean section compared with 3% in all deliveries.

Discussion

In this study 25% of stillbirths were considered to be avoidable on the basis of a retrospective analysis of medical records alone. Using Baird's clinico-pathological classification (Barron & Thomson 1983), all 'avoidable' deaths were categorized under mechanical causes, among which prolonged labour was a predominant feature; 85% of these had a normal birthweight.

Recently, a revised classification has been proposed, largely because new technologies such as intensive neonatal care (for the very-low-birthweight infant) and ultrasound (for the detection of intrauterine growth retardation) demand adaptations of the old classification (Whitfield *et al.* 1986). As these technologies are not generally available in African countries, the Baird classification remains useful to shed light on perinatally related wastage. In our opinion, it also provides more insight into avoidable factors than does another classification, proposed by Wigglesworth (1980), which is based on birthweight and simplified pathological subgroupings.

Amniotic fluid infections have been shown to be the most frequent cause of perinatal mortality in Ethiopia and South Africa (Ross *et al.* 1982). Due to lack of microbiological and autopsy facilities, this could not be investigated in this study. Amniotic fluid infections are important, because they may be related to zinc deficiency and to lowered bactericidal activity of amniotic fluid (Naeye & Ross 1982). There is a need for an investigation of the prophylactic effect of zinc supplementation and nutrition in general (Villa Elizaga & Da Cunha Ferreira 1985). There was a significant reduction in perinatal mortality, by 45%, after the hospital's obstetric policy was changed. It is not easy to interpret this decrease, because there may be many confounding factors, including differences in patient selection and transport facilities during the two periods under investigation. The percentage of hospital births in the region did not differ between the two periods, being approximately 25% of all births (van Roosmalen 1988).

The difference could not be explained by differences in parity, birthweight and the prevalence of obstetric complications such as breech and twin delivery, which are known to increase perinatal mortality. Although the birthweight distribution of twins differed significantly between the two periods, this could account for only a very small amount of the overall decrease in perinatal mortality. The change of policy did not result in more high-risk pregnancies in hospital. The decrease in perinatal mortality is therefore more likely associated with the quality of obstetric care in the hospital.

Perinatal mortality in babies with birthweights ≥2500 g was halved, and this is generally accepted as an indicator of the quality of obstetric care (Chalmers 1980).

The policy changes were not based so much on technological advances, as on the prevention of prolonged labour, the detection of fetal distress at an earlier point and better selection of women with high-risk pregnancies in the district's health centres and dispensaries.

Prolonged labour as a cause of perinatal death can be minimized by the use of the partogram (Studd & Thom 1980). Our findings also suggest that by following the guidelines of the partogram, perinatal mortality may be effectively lowered. Vacuum extraction was performed earlier in labour and with better results, even when used for similar indications.

The partogram should be part of MCH (maternal and child health) training. It should be noted, however, that rural health workers find it difficult to use partograms, although one author reported a good performance of MCH aides in Sierra Leone (Leigh 1986). Rural health workers can experience difficulty in plotting the graph correctly, as has been shown for Morley's 'Road to Health Card' in child care (van Roosmalen & van Roosmalen-Wiebenga 1986). Appropriate action must be taken when the alert line is crossed. There is extensive evidence that postponing intervention till the action line is crossed does not have a negative influence on the obstetric outcome (Bird 1978; van der Does *et al.* 1984; Philpott & Castle 1972; Philpott 1982; Studd 1975). The partogram requires the medical staff to institute 'action' at any time of the day and night. Thorough training and adequate supervision are needed to prevent the use of the partogram becoming a mere ritual. Similar criticisms have also been made with respect to growth monitoring by plotting a child's weight on a card without taking action when a child fails to thrive (Editorial 1985).

The introduction of a perinatal mortality review meeting created awareness of the standards of obstetric care as provided by the hospital staff (Keirse 1985). It can be a threatening experience, since it confronts staff with their own shortcomings. The meeting should be chaired by a person who is committed to the sharing of responsibility rather than to the identification of a guilty party. Such a person should be prepared to set an example by adopting such a vulnerable position with regard to his own role, thereby encouraging the others to look into their own shortcomings. Only then will the tendency to sublimate one's own guilt by placing blame on the patient by making such remarks as 'had the woman only come earlier to hospital', or 'had she only been more co-operative' no longer be necessary.

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Histological features of uteroplacental vessels in normal and hypertensive patients in relation to birthweight

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Summary. Placental bed biopsies were obtained during caesarean section from normal, pre-eclamptic and hypertensive pregnancies. Of the 14 biopsies from normal pregnancies 13 showed normal vascular physiological changes in the decidua and in the myometrium. Biopsies from 24 pregnancies complicated by pre-eclampsia showed acute atherosis in 18 and physiological changes limited to the decidua in six; none had normal physiological changes. Biopsies from five hypertensive patients showed all three types of histological changes. The mean birthweight centile was lower in the group with atherosis than in the group with limited and the group with normal physiological changes.

Spiral arteries in the placental bed show important morphological changes which are essential in normal pregnancy and are termed 'physiological changes' (Brosens *et al.* 1967). The disappearance of musculoelastic tissue from the decidual and myometrial spiral arteries is a typical feature of these morphological changes and allows the arteries to reach a diameter of 800 µm. These changes are probably responsible for the low vascular resistance of the placental bed and determine the large increase in blood flow during pregnancy. Recently uteroplacental vascular flow has been studied by continuous and pulsatile wave Doppler ultrasound: flow is high and vascular resistance is low at 20 weeks gestation, when the second wave of trophoblastic endovascular migration is responsible for the extension of physiological changes from the decidual to the myometrial spiral arteries (Campbell *et al.* 1983; Pijnenborg *et al.* 1981).

Lack of physiological changes beyond the deciduo-myometrial junction has been found in association with pre-eclampsia and other pathological conditions of pregnancy and is believed to result from failure of the second wave of trophoblastic invasion at 20 weeks (Brosens *et al.* 1972).

Acute atherosis in the uterine arteries of the decidua parietalis (decidua vera), decidua basalis and myometrium has been found in pregnancies complicated by pre-eclampsia alone or superimposed on other pathological conditions of pregnancy (Robertson *et al.* 1967; De Wolf *et al.* 1975). Although it is clear that acute atherosis appears in myometrial vessels which have not undergone physiological changes, opinion differs on the presence of this lesion in the decidual spiral arteries that are normally modified by the

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first trophoblastic invasion and in vessels in the decidua vera.

Various investigators claim to have observed acute atherosis not only in association with pre-eclampsia, but also with intrauterine growth retardation (IUGR), in the lupus-like anti-coagulant syndrome and in pregnancies complicated by diabetes, but further studies are considered necessary (Sheppard & Bonnar 1976; De Wolf *et al.* 1980).

There is now increasing evidence that growth retardation, either idiopathic or secondary to hypertensive disease, is often associated with reduced blood flow to the placenta; this could result from partial or complete failure of cytotrophoblastic invasion into the spiral vessels (Gerretsen *et al.* 1981; Khong *et al.* 1986). We have therefore studied the relation between the histological findings of the placental bed with the clinical diagnosis and infant birthweight.

Subjects and methods

A total of 111 biopsies from the site of placental insertion was obtained in women with normal or pathological pregnancies during caesarean section immediately after the delivery of the placenta. Biopsies were considered suitable for inclusion in the study only if they were taken from the central area of the placental bed which showed the presence of spiral arteries in the decidua and in the myometrium and the presence of interstitial giant cells in adequate number.

All specimens were fixed in Bouin's fluid and embedded in paraffin; 5–7 μm serial sections were cut from each block and stained with haematoxylin and eosin (HE), periodic acid Schiff (PAS), Masson's trichrome, Weigert's elastica and Van Gieson stains.

All the slides were studied by two of the authors (L.M., T.F.), without knowledge of the clinical data, and were classified as: (i) normally extended physiological changes (i.e. physiological changes in vessels in the decidua and myometrium); (ii) limited physiological changes (trophoblastic invasion restricted to the decidual segment of the spiral artery), or (iii) acute atherosis: presence of foam cells in damaged arterial walls and/or vascular lesions characterized by fibrinoid necrosis.

Giant cells were scored +, ++, +++, to make sure that all the biopsies had been taken from the central area of the placental bed. Pre-eclampsia was defined as a persistent elevation of blood pressure (≥ 140/90 mmHg) with proteinuria (≥0·5 g/l) but normal values before pregnancy. Superimposed pre-eclampsia was diagnosed by a rise in blood pressure of >20 mmHg and proteinuria in chronic hypertensive patients. All the patients were followed up in our clinic for the study of hypertensive disease of pregnancy to confirm the clinical diagnosis made during pregnancy. We used the birthweight-for-gestational-age charts developed by Lubchenco *et al.* (1963) to calculate the centile birthweight.

Results

Of the 111 biopsies obtained at caesarean section only 46 (42%) were from the placental bed, which is similar to the proportions reported by others (Gerretsen *et al.* 1981; McFayden *et al.* 1986). These 46 biopsies were obtained from: 14 normal pregnancies delivered at term by elective caesarean section and resulting in babies of appropriate-weight-for-gestational age (AGA); 24 pregnancies complicated by pre-eclampsia either alone (16 patients, one with eclampsia) or superimposed on chronic hypertension (five patients) or on nephropathy (three patients); five pregnancies complicated by chronic hypertension, two complicated by unexplained fetal growth retardation and one complicated by systemic lupus erythematosus (SLE).

Of the 14 physiologically normal pregnancies 13 showed normal physiological changes and one showed physiological changes limited to the decidual portion of the spiral artery and acute necrotizing lesions with foam cells in the small basal arteries supplying the decidua which normally do not undergo physiological changes.

The same features were found in another woman who had normal blood pressure and no proteinuria but fetal growth retardation was demonstrated by ultrasound; she was delivered by caesarean section at 34 weeks when there was placental abruption affecting more than one-third of the placental attachment. In the other woman with fetal growth retardation, not associated with hypertensive disease, the physiological changes extended normally into the myometrial segments of the arteries. The physiological changes in the patient with SLE who had a normal pregnancy and a normal outcome were limited to the decidua.

Of the 24 patients with pre-eclampsia, alone or superimposed, six showed physiological changes limited to the decidual spiral arteries but no vasculopathies, whereas 18 had acute atherosis in addition to the physiological changes restricted to decidual segments. In effect, none of the pre-eclamptic pregnancies showed physiological changes normally extended to the myometrial segments of spiral arteries.

In two chronically hypertensive women without pre-eclampsia, the physiological changes were normal, in two others they were limited to the decidua and only one patient showed acute atherosis. This last patient was delivered by caesarean section at 34 weeks because of fetal growth retardation and the infant weighed 1900 g.

Table 1 shows the distribution of histological features of the spiral arteries for all the patients in this study.

The mean birthweights were 1984 g in the group with acute atherosis, 2458 g in the group with only limited physiological changes, and 3193 g in the group with normal physiological changes, but as the mean gestational age at delivery was quite different in the three groups, we analysed the infant birthweights in relation to the gestational age (Lubchenco *et al.* 1963) and these data were correlated to the histological features of the placental bed.

All women with atherosis and also those with limited physiological changes had lower birthweight-centile distributions (birthweight related to gestational age) than the women with normal physiological changes (Fig.1).

The number of infants with birthweights above the 50th centile was significantly higher ($P=0{\cdot}009$, Fisher's exact test) in the group with physiological changes (12 of 16) than in the group with atherosis (4 of 19) but not significantly different from the group with inadequate physiological changes (4 of 11).

Discussion

All the biopsies were confirmed to be from the central area of insertion of the placenta, as shown by the giant cell scores, and all had spiral arteries in the decidua and in the myometrium; with these criteria only 42% of the biopsies were considered suitable to be included in our study Our low success rate, compared with a rate of 70% reported by Robertson *et al.* (1986), may be because in our institution biopsies were not always performed by the same member of staff. Nevertheless, rates similar to ours have been reported by other groups (Gerretsen *et al.* 1981; McFayden *et al.* 1986). In all but one of the normal pregnancies that resulted in babies with weights appropriate-for-gestational-age, the spiral arteries in the decidua and in the myometrium were transformed into uteroplacental vessels, with fully developed physiological changes, indicating that a normal interaction between maternal and trophoblastic tissues had occurred, confirming the results of other investigators (Brosens *et al.* 1967; Gerretsen *et al.* 1981; McFayden *et al.* 1986).

Physiological changes limited to the decidua or atherosis or both were characteristic features of pathological pregnancies: 29 of the 32 complicated pregnancies had either no physiological changes in myometrial spiral arteries ($n=10$) or had atherosis ($n=19$). The presence of arterial lesions or the limitation of physiological changes to the decidua in these pregnancies confirms the

Table 1. Histological features of spiral arteries in 46 placental biopsies in relation to clinical diagnosis

Clinical diagnosis	*n*	Classification of physiological changes: Normal	Inadequate	Inadequate + acute atherosis
Normal pregnancies	14	13	1	—
Chronic hypertension	5	2	2	1
Pre-eclampsia	16	—	4	12
Superimposed pre-eclampsia	8	—	2	6
SLE*	1	—	1	—
Fetal growth retardation	2	1	1	—

* SLE, Systematic lupus erythematosus.

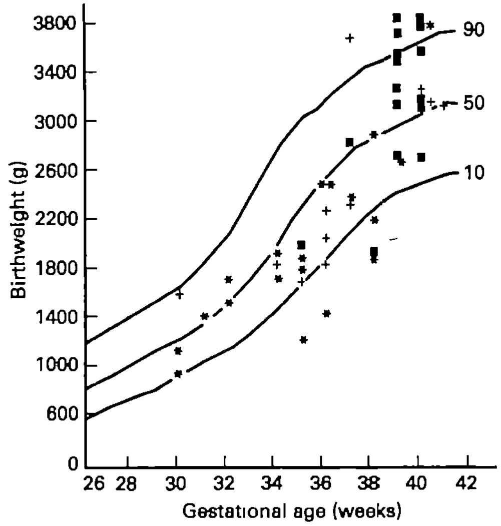

Fig. 1. Birthweight and gestational age in 16 pregnancies with normal physiological changes (■), 11 with limited physiological changes (+); and 19 atherosis (*) superimposed on the birthweight centile charts developed by Lubchenco *et al.* (1963).

importance of performing an extensive and routine study of the placental bed to develop our understanding of the pathophysiology of many complications of pregnancy, such as repeated miscarriage, fetal growth retardation or unexplained fetal death. They may all be different clinical expressions of defective placentation due to the inhibition of the second wave of intravascular trophoblastic migration (Robertson *et al.* 1986; Khong *et al.* 1986).

Only three of the 32 pathological pregnancies showed normal physiological changes; two of them were complicated by chronic hypertension without superimposed pre-eclampsia and resulted in normal weight babies born at term which confirms that hypertension alone does not necessarily impair the normal maternal–trophoblastic interaction. The other pathological pregnancy with physiological changes was complicated by fetal growth retardation not associated with hypertensive disease; the baby's birthweight was <5th centile. The other pregnancy complicated by unexplained fetal growth retardation showed limited physiological changes.

The association between small-for-gestational-age and the anatomy of the placental bed is controversial. Some investigators reported atherosis in almost all cases (Sheppard & Bonnar 1976), others claim to have observed vascular intimal fibrous thickening (Hustin *et al.* 1983); limitation of physiological changes without necrotizing lesions has also been reported by De Wolf *et al.* (1980). Recently, Khong *et al.* (1986) showed that in SGA not associated with hypertension, the trophoblastic vascular invasion can be inadequate (limited to the decidua) or with fewer vessels transformed into utero-placental arteries, or both, implying that apparently normal physiological changes can also be found in some pathological pregnancies. This means that the features of one or a few spiral arteries in a placental bed biopsy may not always be representative of the overall complex maternal vascular response to placentation.

Our data show that the distribution of birthweight centiles differs between the group with atherosis, the group with normal physiological changes and the group with limited physiological changes. This confirms the importance of physiological changes in lowering vascular resistance and facilitating an adequate blood flow (McFayden *et al.* 1986). In many patients with atherosis or limited physiological changes, the weight of the newborn was appropriate-for-gestational-age (AGA). We would emphasize that 60% of our pathological pregnancies (19 of 32) had elective preterm deliveries by caesarean section because of fetal distress, severe pre-eclampsia or fetal growth retardation. All these pregnancies would have been particularly at risk for SGA if they had been allowed to continue to term. On the other hand, we also saw acute atherosis or limited physiological changes or both in patients with pre-eclampsia, SLE and hypertension who gave birth to babies of normal weight at term. This suggests that the association between birthweight and the morphology of the placental bed is not always clear-cut and that other factors are also involved (Khong *et al.* 1986).

Atherosis has been claimed to occur only in vessels that have not undergone physiological changes, but various groups have reported the presence of foam cells in vessels of the decidua with normal physiological changes (Sheppard & Bonnar 1976; McFayden *et al.* 1986). In our biopsies from the placental bed and from the basal plate (not reported here) we had some specimens with obvious foam cells in decidual arteries that had been normally modified by trophoblastic invasion, but we never observed atherosis associated with physiological changes in myometrial arteries. Absence of vascular changes by the second wave of trophoblastic invasion could result in the maintenance of high vascular resistance after 16 weeks gestation and predispose to the development of pathological conditions such as fetal growth retardation and pre-eclampsia; these conditions could be further complicated by the appearance of necrotizing vascular lesions such as acute atherosis severely affecting the uteroplacental blood flow.

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Comparison between mefenamic acid and danazol in the treatment of established menorrhagia

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Summary. Forty women with established menorrhagia were treated with either mefenamic acid (500 mg thrice daily for 3–5 days in two cycles) or danazol (100 mg twice daily for 60 days) in an open parallel group randomized study. Mefenamic acid reduced mean menstrual blood loss from 160 ml to 127 ml (20%, $P<0.01$). Danazol reduced mean menstrual loss from 163 ml to 65 ml (60%, $P<0.001$). The percentage reduction in menstrual blood loss was significantly greater in the danazol group than in the mefenamic acid group, but the adverse side-effects occurred significantly more often in the danazol group (75%) than in the mefenamic acid group (30%, $P<0.005$). Overall, approximately half the women in each group were prepared to continue with the treatment they received to reduce their menstrual bleeding.

Excessive menstrual bleeding is a common complaint and the major cause of iron deficiency anaemia in the UK (Cohen & Gibor 1980). Medical treatment of menorrhagia and co-existing related symptoms should ideally be safe, effective and have high patient acceptability. We performed an open parallel group randomized study to compare the efficacy of mefenamic acid with danazol in 40 patients with unexplained excessive menstrual bleeding (menstrual blood loss >80 ml). This investigation is the first comparative study of these drugs in the treatment of established menorrhagia.

Subjects and methods

Seventy healthy parous women with a history of excessive menstrual bleeding gave informed consent to participate in the study which had been approved by the joint ethics committee of St James's Hospital, Dublin. Menstrual blood loss was measured using the alkaline haematin method (Hallberg & Nilsson 1964). Only 41 of the 70 women (59%) had objective evidence of menorrhagia. One woman withdrew for personal reasons, and the final investigation involved 40 patients. Their mean age was 37·8 years, parity 3·7, and 28 complained of dysmenorrhoea (Table 1). None had any abnormality on clinical and gynaecological examination. All were diagnosed as having dysfunctional uterine bleeding based on clinically normal pelvic organs and the absence of any endometrial pathology at diagnostic curettage within 3 to 12 months before the study.

Menstrual blood loss was initially measured in two control cycles. The assay method was validated by measuring known amounts of blood (5–20 ml, $n=16$) placed on the pads. The recovery ranged from 97% to 112% (mean 105%). During the second cycle an 8–10 ml menstrual blood sample was obtained through a uterine catheter on day 2 of menstruation for analysis of coagulation, fibrinolytic and prostaglandin activities (to be reported elsewhere). The vol-

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Table 1. Demograpic data for 40 women with menorrhagia

	Mefenamic acid group (n=20)	Danazol group (n=20)	Total (n=40)
Age (years)	38·2 (23–48)	37·2 (26–45)	37·8 (23–48)
Parity	3·9 (1–7)	3·5 (1–7)	3·7 (1–7)
No. with dysmenorrhoea	13	15	28

Results are mean (range) values.

ume of blood collected through the catheter was added to the volume estimated by the extraction process to calculate the total menstrual blood loss of the cycle. After collection of samples in cycle 2, the 40 women with menstrual blood loss >80 ml were assigned to receive one of two treatments according to a prepared randomization code. Twenty patients, mean age 38·2 years, were treated with mefenamic acid (Ponstan, Parke-Davis), 500 mg three times daily for 3–5 days, beginning at the onset of menstrual flow in the next two cycles (cycles 3 and 4). Twenty patients, mean age 37·2 years, received danazol (Danol, Winthrop Laboratories), 100 mg twice daily for 60 days (cycles 3 and 4), beginning on the last day of menstruation in cycle 2. Patient compliance was checked by counting the tablets/capsules remaining in the container at the end of each cycle. Menstrual blood loss was assessed again in the two treatment cycles (3 and 4), the catheter test being repeated in cycle 3.

Subjective assessment of dysmenorrhoea was scored on a scale from 0 to 3 (0=no symptoms; 1=mild; 2=moderate; 3=severe). Side-effects were recorded after each cycle by asking the question: ‘Do you think the treatment has upset you in any way?’ Reported symptoms were recorded giving: type of effect, severity (0–3), time to onset, duration and frequency. At the end of the study, patient acceptability was assessed by asking: ‘Would you be prepared, if required, to continue with this treatment?’ If the answer was ‘No’, the reason(s) was recorded.

The Mann–Whitney and Wilcoxon signed rank tests were used for statistical analysis of unpaired and paired data.

Results

Untreated cycles

For the 20 women in the mefenamic acid group, insertion of the uterine catheter in cycle 2 was associated with a 21% reduction of menstrual blood loss compared with cycle 1 (138·7 ml *vs* 174·4 ml). The corresponding reduction for the 20 women in the danazol group was 19% (146·5 ml *vs* 179·8 ml). When menstrual blood loss in cycle 2 was compared with cycle 1 for all 40 patients in the study, a significant (P<0·001) reduction was obtained, but there was no significant difference between the two study groups.

Treated cycles

Table 2 shows the measured menstrual blood losses after treatment with mefenamic acid and danazol. The results in the mefenamic acid group are based on 19 subjects as one woman with side-effects was withdrawn. In this group, the mean of the individual losses in the first two

Table 2. Menstrual blood loss (in ml) in untreated and treated cycles

	Untreated		Treated	
	Cycle 1	Cycle 2*	Cycle 3*	Cycle 4
Mefenamic acid (n=19)				
Mean (SD)	177·6 (80·8)	141·6 (85·9)	115·8 (71·9)	139·1 (85·4)
Mean (SD)	159·6 (77·6)		127·3 (75·4)	
Mean difference Wilcoxon text			32·3 (20%)	(P=0·004)
Danazol (n=20)				
Mean (SD)	179·8 (88·5)	146·5 (76·5)	87·3 (61·3)	42·4 (39·4)
Mean (SD)	163·1 (77·8)		64·8 (43·8)	
Mean difference Wilcoxon test			98·3 (60%)	(P=0·0001)

Mefenamic acid *vs* danazol: Mann–Whitney U-test (% changes) P=0·0004.

* Catheter inserted.

cycles (control cycles) was significantly higher than that in the two treatment cycles (159·6 ml *vs* 127·3 ml), a 20% reduction ($P<0·01$). In three women menstrual blood loss was higher on treatment. The overall reduction was 18% in the first treatment cycle and 22% in the second.

In the danazol group the mean of the individual losses in cycles 1 and 2 (control cycles) was significantly higher than in treatment cycles 3 and 4 (163·1 ml *vs* 64·8 ml, a reduction of 98·3 ml or 60·3%, $P<0·001$). The overall reduction was 40% in the first treatment cycle and 76% in the second. The reduction in menstrual blood loss was significantly greater after treatment with danazol than with mefenamic acid ($P<0·001$).

Figure 1 illustrates the percentage changes in menstrual blood loss between the two control cycles and the two treatment cycles for each patient. The mean change was 22·3% on mefenamic acid and 56·0% on danazol.

There was no significant effect on the mean duration of menstruation in the mefenamic acid group (cycle 1, mean 6·0, SD 1·3 days; cycle 4, mean 5·9, SD 1·1 days) or the danazol group (cycle 1, mean 6·0, SD 1·1 days; cycle 4, mean 4·8, SD 2·9 days). There was no significant effect of either treatment on the cycle length: control cycles 1 and 2, mefenamic acid (27·6, SD 2·0 days), danazol (27·9, SD 3·0 days), treatment cycles 3 and 4, mefenamic acid (26·8, SD 3·3 days), danazol (34·3, SD 21 days). Two women treated with danazol had exceptionally long cycles of 81 and 96 days in cycle 4.

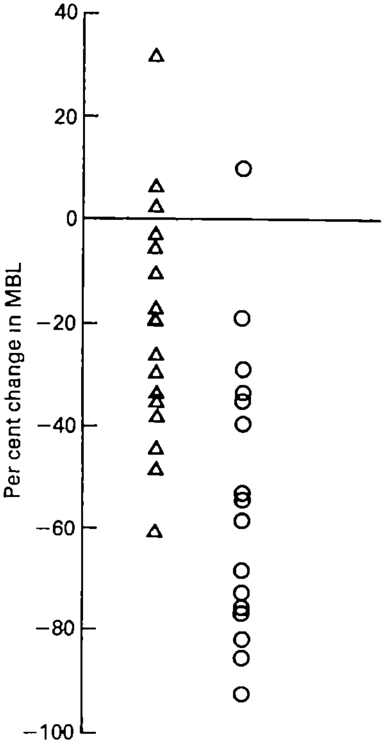

Fig. 1. Percentage change in menstrual blood loss (MBL) between pretreatment cycles 1 and 2 and treatment cycles 3 and 4 shown for individual women treated with (Δ) mefenamic acid or (O) danazol. Mean % change is −22·3% in the mefenamic acid group and −56·0% in the danazol-treated group.

Dysmenorrhoea

Mefenamic acid improved dysmenorrhoea in 10 of 13 women; the mean symptom score was reduced from 1·9 (SD 0·8) in cycle 1 to 1·1 (SD 0·9) in cycle 4 ($P<0·01$). Danazol improved symptoms in 12 of 15 women; the mean symptom score was reduced from 1·8 (SD 0·8) in cycle 1 to 0·7 (SD 1·1) in cycle 4 ($P<0·01$). There was no statistically significant difference between the two therapies.

Side-effects

Side-effects of therapy are shown in Tables 3 and 4. Six (30%) women treated with mefenamic acid reported side-effects, compared with 15 (75%) in the danazol group ($P<0·005$, χ^2). Danazol-treated women reported 51 events compared with 11 in the mefenamic acid group.

Four patients treated with mefenamic acid experienced adverse effects, most commonly nausea/vomiting and diarrhoea. More serious adverse effects were encountered in the danazol group. Musculoskeletal pains, flushes, dizziness, vertigo and backache occurred intermittently throughout therapy. More persistent symptoms included behavioural changes, acne, tiredness and a feeling of being 'off-colour'. Breast atrophy, hirsutism and hoarseness developed during the second month of treatment. The most common side-effects were headaches and nausea. One patient considered weight gain an adverse event although all patients in this group gained between 0·2 and 3·8 kg (mean 2·02 kg). They all returned to their pretreatment weights within 3 months after discontinuing therapy.

Patient acceptability of treatment

At the end of the study nine women in the mefenamic acid group were unwilling to con-

Table 3. Side-effects in 20 patients treated with mefenamic acid*

Side-effects	Side-effects No. of events	Mild	Moderate	Severe
Nausea/vomiting	4	2	—	2
Abdominal discomfort	2	1	—	1
Diarrhoea	1	—	—	1
Headache	2	1	1	—
Dizziness	1	—	—	1
Fluid retention	1	—	1	—
Total	11	4	2	5

* Overall six women reported side-effects.

tinue therapy because of inadequate reduction in blood loss, and two of them also gave adverse side-effects as a second reason. Ten patients in the danazol group refused to continue, one because of inadequate reduction in blood loss and eight because of adverse effects, one of whom also gave cycle alteration as a second reason. One patient gave cycle alteration as her only reason.

Discussion

In this study, significant reductions in blood loss were achieved with both mefenamic acid (20%) and danazol (60%), the improvement being significantly greater ($P<0{\cdot}001$) with danazol.

Previous studies on mefenamic acid therapy for menorrhagia (Anderson *et al.* 1976; Haynes *et al.* 1980; Fraser *et al.* 1981; Muggeridge & Elder 1983) reported greater reductions in menstrual blood loss, ranging from 24% (Muggeridge & Elder 1983) to 44·5% (Haynes *et al.* 1980). In our study, blood loss increased in three patients, others have also reported increases in some women (Haynes *et al.* 1980; Fraser *et al.* 1981; Muggeridge & Elder 1983). In agreement with our results, Haynes *et al.* (1980) and Guillebaud *et al.* (1978) reported no effect of therapy on duration of menstruation but Fraser *et al.* (1981) found a significant reduction.

In both treatment groups, blood loss was approximately 20% lower in cycle 2 (catheter test cycle) compared with cycle 1. This reduction appears to have been the effect of the catheter removal of the menstrual blood.

Danazol reduced menstrual blood loss by 40% in the first treatment cycle and by 76% in the second; very similar results were reported by Chimbira *et al.* (1980) who found a reduction of 73% in the second cycle, using the same drug dosage. Similarly, duration of menstruation and mean cycle length were not significantly different during treatment with danazol although two patients found the unpredictable cycle range (14–96 days) unacceptable.

Both treatments were highly effective in relieving dysmenorrhoea. Mefenamic acid reduced intrauterine pressure in primary dysmenorrhoea (Pulkkinen & Kaihola 1977; Smith & Powell 1982), which is associated with

Table 4. Side-effects in 20 patients treated with danazol*

Side-effects	Side-effects No. of events	Mild	Moderate	Severe
Due to pituitary-gonadal inhibition				
Breast atrophy	3	—	1	2
Breast pain	2	1	1	—
Flushes	2	1	1	—
Due to androgenic activity				
Acne	3	2	1	—
Hirsutism	1	1	—	—
Hair loss	1	—	1	—
Weight gain	1	—	1	—
Increased libido	1	—	1	—
Hoarseness	1	1	—	—
General effects				
Irritability/aggression	3	—	2	1
Depression	2	1	1	—
Emotional lability	1	—	1	—
Dizziness	2	—	2	—
Vertigo	1	—	—	1
Headache	8	5	3	—
Nausea/vomiting	6	3	2	1
Adominal discomfort	1	—	1	—
Musculoskeletal pains	5	3	2	—
Backache	2	—	2	—
Tiredness	2	—	1	1
Off-colour	2	—	2	—
Blurred vision	1	—	1	—
Total	51	18	27	6

* Overall 15 women reported side-effects.

increased levels of prostaglandin $F_{2\alpha}$ in the endometrium (Pickles *et al.* 1965; Willman *et al.* 1976). Whether intrauterine pressure is increased in dysmenorrhoea associated with unexplained menorrhagia is unknown.

Unacceptable side-effects were experienced by two patients treated with mefenamic acid, one of whom withdrew because of severe gastrointestinal symptoms and dizziness. In previous trials (Anderson *et al.* 1976; Guillebaud *et al.* 1978; Haynes *et al.* 1980; Fraser *et al.* 1981; Muggeridge & Elder 1983), four of 145 patients (3%) dropped out because of adverse effects. In our study 30% of the women experienced side-effects. These results are similar to those of Jakubowicz *et al.* (1984), who reported minor side-effects in 26% of 80 women treated with mefenamic acid for premenstrual syndrome.

Although none of the danazol-treated patients withdrew from our study, eight (40%) experienced unacceptable side-effects. Most had diverse symptoms all of which resolved after discontinuing therapy, although one patient considered her breast size to be markedly smaller 10 months later. Chimbira *et al.* (1980) reported 24 side-effects in 16 patients treated with the same dosage, and 33% experienced somnolence, fatigue and headaches.

Despite the obvious differences in efficacy and adverse effects, overall patient acceptance of the treatment was similar. Approximately half the patients did not wish to continue with the treatment; nine in the mefenamic acid group due to lack of efficacy, and eight in the danazol group due to unacceptable side-effects despite a reduction in blood loss.

This study demonstrates that it is important to consider both efficacy and patient acceptability when selecting the most appropriate agent for the treatment of menorrhagia. Although mefenamic acid is less effective in reducing menstrual blood loss, the short dosage regimen, the fewer adverse effects and much lower cost make it a reasonable initial treatment.

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Cerebral Doppler ultrasound of the human fetus

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Summary. Maximal flow velocity waveforms were recorded in the internal carotid artery (ICA), middle cerebral artery (MCA), posterior cerebral artery (PCA) and anterior cerebral artery (ACA) in 55 normal pregnancies and 14 complicated by intrauterine growth retardation between 25 and 41 weeks gestation. In normal pregnancy, acceptable flow velocity waveforms were obtained in the ICA in 89%, in the MCA in 91%, in the PCA in 58% and in the ACA in 64%. A decrease in pulsatility was observed in all four intracranial arteries during the latter weeks of gestation. In growth-retarded pregnancies, pulsatility in all vessels was significantly reduced compared with normal pregnancy, suggesting participation of all major intracranial arteries in a brain-sparing effect in the presence of chronic fetal hypoxia.

Recently, duplex sonography, a combination of high-resolution real-time and pulse-gated directed Doppler ultrasound, was introduced in the study of blood flow velocity waveforms in the human fetal internal carotid artery (Wladimiroff *et al.* 1986). Direct evidence for the occurrence of a brain-sparing effect in cases of intrauterine growth retardation (IUGR) due to placental insufficiency was provided (Wladimiroff *et al.* 1987; Arduini *et al.* 1987). In contrast to the umbilical artery, however, pulsatility index (PI) calculations in the internal carotid artery exhibited a poor sensitivity in identifying IUGR (Wladimiroff *et al.* 1988). The objective of the present study was twofold: first, to study basic flow patterns in the basal cerebral arteries in the healthy human fetus; second, to assess the haemodynamic status of the growth-retarded human fetus.

Subjects and methods

A total of 14 patients with fetal growth retardation was referred to our ultrasound unit between February and July 1987. Gestational age ranged between 27 and 37 weeks. During the same study period 55 pregnant subjects with uncomplicated pregnancies were randomly selected to serve as controls. Here, gestational age varied between 25 and 41 weeks. Each patient was certain of the date of onset of her last menstrual period.

Normal pregnancies were defined by normal fetal biparietal diameter (BPD), head circumference and upper abdominal circumference measurements according to the nomogram by Campbell (1976) and by birthweight between the 10th and 90th centile for gestational age according to Kloosterman's tables (Kloosterman 1970) corrected for parity and fetal sex. Intrauterine growth retardation (IUGR) was

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defined as a growth pattern resulting in a clinical discrepancy of >2 weeks on fundal height on two successive antenatal appointments, and ultrasound findings of upper abdominal circumference measurements below the 5th centile in association with normal or reduced head circumference measurement. Head to abdominal ratio values were calculated as described by Campbell & Thoms (1977). IUGR was retrospectively confirmed by the birth of an infant under the 5th centile for gestational age according to Kloosterman's tables (Kloosterman 1970) corrected for parity and fetal sex.

Of the 14 pregnancies with IUGR, 10 (71%) exhibited an elevated head to abdominal ratio; 7 (50%) presented with pregnancy-induced hypertension; in the other seven there was no overt maternal or fetal disease. There were four perinatal deaths. In the pregnancies with IUGR, the mean lag time between blood flow velocity recording and delivery was 11 days (range 1–47).

A combined mechanical sector and pulsed Doppler system (Diasonics CV 400) with a carrier frequency of 3·5 and 3 MHz was used for blood flow velocity measurements in the internal carotid and basal cerebral arteries.

The maximum flow velocity waveform in the internal carotid artery (ICA) was obtained at the level of the bifurcation into the middle and anterior cerebral artery, as described previously (Wladimiroff *et al.* 1986). The sample volume was set at 4 mm and the high-pass filter at 100 Hz. A schematic display of the anatomical location of the basal cerebral arteries (anterior, middle and posterior arteries) is presented in Fig. 1. An axial view of the fetal head was obtained at the level of the cerebral peduncles. The arterial pulsations of the right and left middle cerebral artery (MCA) can be seen running from their origin of the internal carotid artery into the lateral sulcus over the anterior perforated substance and disappearing onto the cerebral fossa between the temporal lobe and insula. The sampling cursor was placed into the pulsating artery in the lateral sulcus, closest to the Doppler transducer. The posterior cerebral arteries (PCA) can be seen coursing around the midbrain in the ambient cistern. Flow velocity recordings were made at the level of the transverse cerebral fissure on the side of the midbrain closest to the Doppler probe. Finally, using the pulsating internal carotid artery as landmark, the sampling cursor was moved anteriorly along the midline over a distance of approximately 2 cm. The sample volume was enlarged to 12 mm, thereby allowing the flow velocity waveform of both anterior cerebral arteries (ACA) to be recorded, and thus facilitating the initial identification of flow in these vessels. The sample volume was then reduced to 4 mm to exclude one of the two signals. For all four vessels, the angle between the Doppler interrogation beam and flow direction was always kept below 60°. The degree of pulsatility of the waveform was quantified by calculating the pulsatility index (PI) according to Gosling & King (1975) over at least four consecutive cardiac cycles. All measurements were performed with the woman in the semirecumbent position and during fetal apnoea, since high-amplitude fetal breathing modulates the blood flow velocity waveforms (Marsal *et al.* 1984).

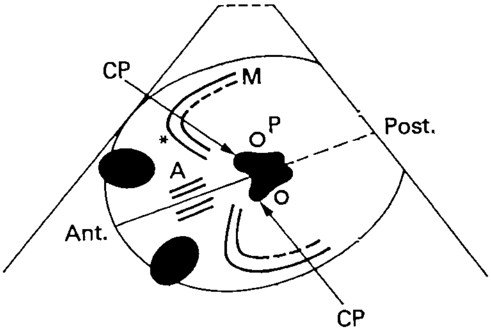
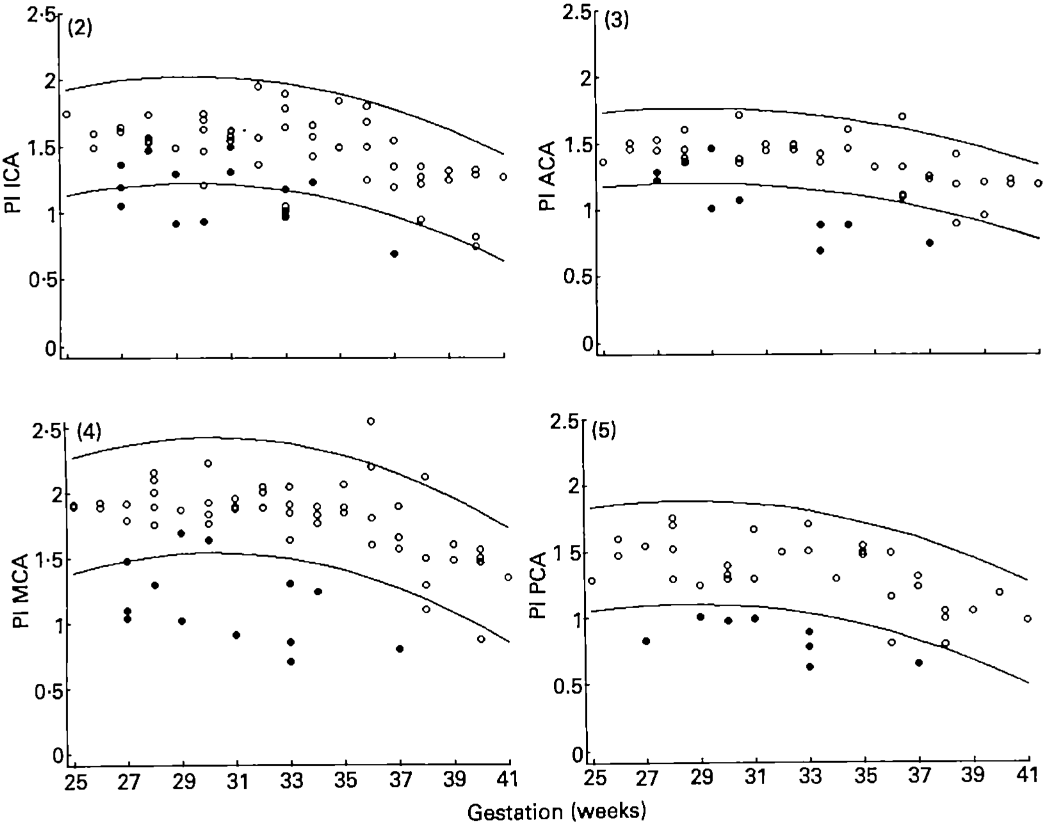


Fig. 1. Schematic representation of the ultrasound cross-section of the fetal head with the anatomical location of the anterior (A), middle (M) and posterior (P) cerebral arteries. CP, Cerebral peduncle, *, position of sample volume for middle cerebral artery measurement.

Statistical analysis included investigation of the relations between the PI values and gestational age by polynomial regression (Deter *et al.* 1982). The percentage of pregnancies with IUGR that had abnormal PI levels was compared with the corresponding percentage of normal subjects using Fisher's exact test.

Results

Acceptable flow velocity waveforms for PI calculations were obtained in the ICA in 49 (89%), in the MCA in 50 (91%), in the PCA in 32 (58%) and in the ACA in 35 (64%) of the normal subjects. The individual data plots of the PI



Figs 2–5. Pulsatility index values from the fetal internal carotid artery (PI ICA; Fig 2), anterior cerebral artery (PI ACA; Fig. 3), middle cerebral artery (PI MCA; Fig. 4) and posterior cerebral artery (PI PCA; Fig. 5) for normal pregnancies (O) and pregnancies complicated by fetal growth retardation (●) relative to gestational age Plotted curves represent normal limits (±2 SD).

values from these intracranial vessels are presented in Figs 2–5.

Fitting polynomials, it appeared that mean PI values of all four vessels could not be described by linear equation, but that also quadratic components of age were needed (Table 1). For none of the parameters did the cubic component of age reach statistical significance. Normal limits, taken as fitted mean values ±2 SD, are presented in Figs 2–5. The standard deviations of the measured values around the fitted curves for PI in the ICA, MCA, PCA and ACA were 0·20, 0·22, 0·19 and 0·14 respectively.

Figures 2–5 also display the data points from the IUGR study. PI values were obtained in the ICA in all 14 pregnancies, in the MCA in 13, in the PCA in eight, and in the ACA in 10. In all four vessels the percentage of IUGR pregnancies with a PI value below the 2 SD cut-off level was significantly ($P<0·001$) greater than the corresponding percentages for normal subjects. The sensitivity in identifying IUGR at the 2 SD cut-off level was 57% for the ICA, 85% for the MCA, 100% for the PCA and 60% for the ACA.

Discussion

The normal waveform in the fetal internal carotid and basal cerebral arteries in the third trimester of pregnancy always displays forward flow. These large intracranial arteries, therefore, seem to serve a universally low-resistance vascular bed in the human fetal brain. The ICA and MCA always produced the strongest signals, which is reflected in the success rate in obtaining acceptable flow velocity waveforms in these vessels. Signal intensity of the PCA and ACA was frequently weak. Optimal flow velocity waveforms were, therefore, more difficult to obtain. Similar problems were met by Aaslid *et*

Table 1. Results of least-squares quadratic regression of ICA, MCA, PCA and ACA PI values on age

	Constant	Coefficient of linear term	Coefficient of quadratic term
PI ICA	−2·26 (1·73)	0·26 (0·11)	−0·0044 (0·0016)
PI MCA	−3·44 (1·77)	0·36 (0·11)	−0·0060 (0·0016)
PI PCA	−1·74 (2·00)	0·23 (0·12)	−0·0040 (0·0019)
PI ACA	−0·66 (1·36)	0·15 (0·08)	−0·0027 (0·0013)

Standard errors of regression coefficients are in parentheses.
PI, Pulsatility index; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery

al. (1982) who studied Doppler signals from the PCA and ACA in the same scanning plane in healthy adults. In normal pregnancy, PI values in the MCA were markedly higher than in the other intracranial vessels. This is explained by the rapid systolic upstroke in the flow velocity waveform followed by a sharp velocity decline during diastole. The reduction in PI observed in all four vessels during the latter weeks of normal pregnancy was predominantly determined by an increase in end-diastolic flow velocity. This is in agreement with earlier findings in the fetal ICA (Van den Wijngaard *et al.* 1988), ACA (Arbeille *et al.* 1987) and MCA (Woo *et al.* 1987; Kirkinen *et al.* 1987). The physiological mechanism responsible for these flow velocity waveform changes is still unknown. Recently a reduction in Po_2 was established in the umbilical artery through cordocentesis during this period of gestation (Soothill *et al.* 1986). On the basis of this Po_2 reduction, we postulate that the aforementioned increase in end-diastolic flow velocity may reflect a haemodynamic redistribution favouring blood supply to the brain.

In IUGR there is a marked reduction in PI in the ICA and basal cerebral arteries. These changes are predominantly due to an increase in end-diastolic flow velocity and confirm earlier data (Wladimiroff *et al.* 1987; Arduini *et al.* 1987) suggesting a brain-sparing effect in the presence of IUGR. These findings imply that the major intracranial arteries all participate in the circulatory redistribution favouring brain perfusion in the presence of chronic fetal hypoxia. The limited number of IUGR pregnancies in this study does not allow meaningful statistical comparisons regarding sensitivity in detecting IUGR. However, there seems to be an indication that especially the MCA and PCA, both responsible for blood supply to the brainstem areas, are highly sensitive indicators of fetal compromise. The sensitivity of the PI in the ICA seems to be poor (57%), as has been demonstrated in an earlier study (Wladimiroff *et al.* 1988) (45%). During the last trimester the fetal head usually faces laterally, and then the optimal vessel for Doppler measurements is the MCA (Kirkinen *et al.* 1987). The combination of easy accessibility and promising sensitivity warrants a further study of the significance of PI determinations in the MCA for assessing fetal growth retardation.

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Preterm labour in twin pregnancies: can it be prevented by hospital admission?

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Summary. Women attending a twin pregnancy antenatal clinic underwent cervical palpation to calculate a cervical score by subtracting dilatation from length. Those with a score of −2 or less at or before 34 weeks are at especially high risk of preterm labour. A total of 139 such women were randomly allocated either to receive bed-rest in hospital or to continue conventional outpatient management. No beneficial effect of bed-rest could be identified in prolonging twin pregnancy or improving fetal outcome.

Preterm labour in twin pregnancies is common and results in a perinatal mortality rate several times that of singleton pregnancies (Crowther 1987). Although, in Western countries, twin pregnancies occur with a frequency of only 1%, no less than 12% of babies that die during the early neonatal period are from multiple pregnancies (Manlan & Scott 1978). Morbidity is common among survivors (Pearlman & Batton 1988). The ability to predict and then prevent preterm labour in twin pregnancies would therefore be an important advance.

We have shown that cervical assessment by digital examination identifies a group of twin pregnancies at especially high risk of preterm labour (Neilson *et al.* 1988). A score was calculated by subtracting cervical dilatation from cervical length (both in cm) (Houlton *et al.* 1982) and studied in 223 parous women with twin pregnancies who ultimately laboured spontaneously; 76% of those who had a score of −2 or less at or before 34 weeks were delivered preterm, that is before 37 completed weeks gestation. Such effective prediction of preterm labour is, however, only useful if consequent clinical action can result in prolongation of pregnancy or some other effect which improves fetal outcome. Bed-rest in hospital (Hartikainen-Sorri & Joupilla 1984; Saunders *et al.* 1985), cervical cerclage (Weekes *et al.* 1977), and beta sympathomimetic drugs (Marivate & Norman 1982) have not been shown convincingly to improve outcome when used routinely in all twin pregnancies. We have therefore conducted a randomized controlled trial to examine whether bed-rest in hospital, applied selectively to those women at especially high risk of preterm labour (as identified by cervical findings) improves twin pregnancy outcome.

Subjects and methods

The Government and University obstetric services in Harare jointly supervise more than

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Table 1. Characteristics of the two study groups

	Hospitalized group (n=70)	Control group (n=69)
Age (years)	27·1 (5·9)	27·0 (5·7)
Height (cm)	160·0 (6·5)	160·3 (8·1)
Weight at 28 weeks (kg)	68·1 (7·4)	70·6 (11·2)
Previous preterm delivery	12 (17%)	11 (16%)
Nulliparae	2 (3%)	6 (9%)
Gestational age at entry (weeks)	33·3 (1·8)	33·5 (1·8)
Cervical score at entry		
−4	4	0
−3	18	14
−2	48	55

Results are mean (SD) or n(%) values as appropriate.

40 000 deliveries a year, half in 13 clinics staffed by midwives, and half (all high-risk pregnancies) in the central unit at Harare Central Hospital. A special twin pregnancy antenatal clinic was started at the hospital during 1983 at which women attended once a fortnight before 28 weeks and weekly from then on. The cervix was examined digitally at each attendance by one of two of us (C.A.C. or D.A.A.V.) and the cervical score noted. Women with a cervical score of −2 or less at or before 34 weeks were eligible for entry into this trial, which started in 1984. No woman was in labour at entry and tocolytic drugs were not used.

Randomization was formal and used block randomization to provide balanced numbers in the study groups. The researchers involved in allocating the women to the treatment groups were not involved in preparing the randomization schedule. There was no stratification at randomization. With consent, the next in a series of consecutively numbered, opaque, sealed envelopes was opened and the woman allocated according to the enclosed instructions to hospitalization for bed-rest (hospitalized group) or not (control group).

It had been estimated that a trial size of 44 would have an 80% chance (beta error 0·20) of detecting a statistically significant difference at the 5% level (alpha error 0·05) if the preterm delivery rate was reduced from 80% (Neilson *et al.* 1988) to 40%. However, as there are currently no data on which to base confident estimates of the effects of hospitalization in such a high-risk group, as many eligible women as possible were recruited during the time available for the study.

All newborn infants were examined by a paediatrician (C.B.) who was unaware to which group the mother had been allocated. Dubowitz scoring, which has been validated in African populations (Brueton *et al.* 1973; Singer *et al.* 1973; Raghu *et al.* 1981), was used to confirm gestational age at delivery. Preterm was defined as less than 37 completed weeks gestation. Babies were classified as small-for-gestational-age if their birthweight was < the 10th centile by local singleton standards.

Analysis was by Student's t-test or χ^2-test as appropriate.

Results

The process of randomization achieved two groups whose characteristics were comparable in a number of important respects (Table 1).

Results were analysed according to initial allocation and despite (rare) non-compliance. Thus, two of the 70 women allocated for bed-rest did not, in fact, attend the antenatal ward. Their pregnancies are included in the hospitalization group as are a further nine women who required transient leave of absence from the hospital for domestic reasons (mean 9·9 days, SD 6·7). Similarly, 17 of the 69 women in the control group were subsequently admitted to hospital because of pregnancy complications but their

Table 2. Pregnancy outcome

	Hospitalized group (n = 70)	Control group (n = 69)
	Mean (SD)	Mean (SD)
Gestational age at delivery (weeks)	35·8 (1·9)	35·8 (1·9)
Entry-to-study to delivery interval (days)	18·1 (12 9)	17·9 (14·7)
	n(%)	n(%)
Delivery <37 weeks	51 (72·9)	55 (79·7)
Delivery <34 weeks	11 (15·7)	12 (17·4)
Spontaneous labour	69 (98·6)	65 (94·2)
Caesarean section	5 (7·1)	10 (14·5)
Hypertension	7 (10·0)	6 (8·7)
Preterm rupture of membranes	13 (18·6)	8 (11·6)
Other complications	7 (10·0)	5 (7·3)

Table 3. Fetal outcome

	Hospitalized group	Control group
Number of babies	140	138
Stillbirths	1	1
Neonatal deaths	1	1
Apgar score <7		
At 1 min	21 (15·0%)	29 (21·0%)
At 5 min	8 (5·7%)	4 (2·9%)
Birthweight (kg)		
Twin I	2·35 (0·45)	2·25 (0·53)
Twin II	2·40 (0·46)	2·27 (0·47)
Small-for-gestational-age		
Twin I	26 (37·1%)	22 (31·9%)
Twin II	25 (36·7%)	29 (42·0%)
Special care neonatal unit		
Admissions	51 (36·4%)	65 (47·1%)
Duration of stay in days	8·3 (9·0%)	10·9 (11·2%)

Results are mean (SD) or *n*(%) values as appropriate.

details are retained under controls. The mean length of stay in the hospitalized group was 16 days (SD 13·1) and 1·3 days (SD 3·1) in the control group.

Details of pregnancy and of fetal outcome are shown in Tables 2 and 3. We could find no evidence that hospitalization prolonged pregnancy, diminished the frequency of preterm labour, improved fetal outcome or enhanced the rate of fetal growth. Two babies in each group died during the perinatal period—three as a result of intrapartum asphyxia, and one (in the control group) from the effects of immaturity.

Discussion

Preterm delivery of twins is a major perinatal problem which may become more common with the increasing use of techniques such as in-vitro fertilization. In theory, hospitalization could be advantageous in one of two ways—by prolonging pregnancy to achieve greater fetal maturation at the time of delivery and/or by optimizing intrapartum management, to include fetal assessment, by ensuring that labour starts in the hospital. Hospitalization is, however, a costly and socially disruptive procedure for which it is essential to demonstrate benefit in fetal outcome or pregnancy management before recommending its widespread application (Powers & Miller 1979). On the basis of many poorly controlled studies which have been reviewed elsewhere (Grant *et al.* 1982; Crowther & Chalmers 1988) it has been recommended (though not unanimously) that bed-rest in hospital is beneficial for twin pregnancies. By not *randomly* allocating patients to hospitalization, these studies introduced biases because those who declined (or were not offered admission) may well already have been at increased disadvantage when compared with those admitted to hospital.

Two randomized controlled studies of hospitalization of women with twin pregnancies have now been reported. The first, from Finland (Hartikainen-Sorri & Joupilla 1984) reported on 73 pregnancies of which 28 were subjected to planned hospitalization from 29 weeks gestation. The second, a previous study in Zimbabwe (Saunders *et al.* 1985), described 212 pregnancies of which half were allocated to hospitalization from 32 weeks. Neither showed evidence of prolongation of pregnancy by hospitalization. The study we report here differs in two respects from both of the earlier randomized trials, because we applied hospitalization selectively to those women at especially high risk of preterm labour (rather than routinely to all), and because a fixed gestational age for starting hospitalization was not used. The large number of pregnancies in both of our groups which were delivered preterm confirmed, on prospective study, the high positive predictive value (76%) of cervical assessment using the diagnostic criteria which we derived from previous retrospective investigation (Neilson *et al.* 1988). Despite the correct identification of a group at very high risk of preterm labour, we could find no evidence of prolongation of pregnancy as a result of bed-rest in hospital. Bed-rest at home has been recommended as an inexpensive and less disruptive alternative despite the lower likelihood of compliance and the shorter available opportunities for rest. It seems unlikely that this would help prolong twin pregnancies if more intensive rest in hospital does not.

The variable pattern of cervical ripening suggested to us that a fixed time bracket both for cervical assessment and also for hospitalization would not be appropriate. We therefore included any patient who fulfilled the cervical criteria at any time before 34 weeks, and it may be argued that if bed-rest is beneficial it needs to be employed earlier in pregnancy. This hypothesis would need to be tested, as in the current study, by randomized clinical trial.

In conclusion, we have been unable to demonstrate any benefit from bed-rest in hospital. We are obliged to continue to investigate alternative strategies which may help prolong gestation and improve fetal outcome in twin pregnancies.

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Binding of anti-EMA, AGF 4:48 and the lectin UEA-1 to human ovarian carcinomas: histological and clinical correlations

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Summary. The staining reactions of the monoclonal antibodies anti-EMA, AGF 4:48 and the lectin UEA-1 from *Ulex europaeus* were investigated in formalin-fixed, paraffin-embedded sections of 36 primary ovarian carcinomas. The staining patterns were graded and related to tumour type, differentiation, FIGO stage and patient survival. Both antibodies and UEA-1 showed variations in their staining between and within tumours. The staining of mucinous tumours using anti-EMA was significantly less than in non-mucinous tumours. No other significant associations were found between staining grade and the different variables under study. The variations in staining were not demonstrated to have any prognostic significance.

An association has been demonstrated between certain differentiation antigens and neoplastic markers using antibodies against carbohydrate determinants (Feizi 1985). AGF 4:48 is a monoclonal antibody which has been shown to detect one such group, 3-fucosyl-*N*-acetyllactosamine (Howie *et al.* 1984). This has been identified as an embryonic stage-specific antigen in mice (Gooi *et al.* 1981) and is also detected by VEP8, VEP9, My1, SSEA-1 and Ig10 monoclonal antibodies (Howie *et al.* 1984; Walker & Day 1986). It is distributed in a wide range of human tissues (Howie *et al.* 1984; Howie & Brown 1985; Fox *et al.* 1983) and tumours (Fox *et al.* 1983). Studies on human breast using this antibody and the fucose-binding lectin UEA-1 derived from *Ulex europaeus* have shown alterations in fucose-containing glycoconjugates in malignancy (Walker & Day 1986; Walker 1984) but these have no statistically significant influence on survival.

Antibodies to human epithelial membrane antigen (EMA) have been widely used in diagnostic histopathology for the identification of tumours of epithelial origin (Heyderman *et al.* 1985; Cordell *et al.* 1985; Sloane & Ormerod 1981; Pinkus & Kurtin 1985). Anti-EMA (Dako) is a monoclonal antibody raised against a preparation of human milk fat globule membrane protein (Heyderman *et al.* 1985, Cordell *et al.* 1985). The determinant recognized is believed to be carbohydrate in nature. It has

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been found to react with a wide variety of human epithelial cells, both normal and neoplastic, and with mesothelium (Heyderman *et al.* 1985; Cordell *et al.* 1985). To our knowledge its value as a prognostic indicator in ovarian tumours has not been investigated, although breast carcinomas have been studied with the two related monoclonal antibodies, HMFG-1 and HMFG-2 (Berry *et al.* 1985; Rasmussen *et al.* 1982; Wilkinson *et al.* 1984; Turnbull *et al.* 1986).

In this study we have applied anti-EMA, AGF 4:48 and peroxidase-labelled UEA-1 to a range of human primary ovarian carcinomas to determine whether variations in their staining can provide prognostic information.

Materials and methods

Tissues

Sections, 4 μm thick, were cut from representative blocks of 36 primary ovarian carcinomas obtained from patients who had been entered into the West Midlands Ovarian Cancer Group studies at the Birmingham and Midland Hospital for Women and other centres in the West Midlands Region. In 19 tumours material was obtained from patients entered into a single prospective study and who had undergone secondary surgery, in order to study the effect of chemotherapy on surface antigen expression. The additional material came from patients with either endometrioid or clear-cell tumours that had initially been diagnosed at the Birmingham and Midland Hospital for Women in order to provide a similar number of each histological subtype.

Immunohistochemistry

After dewaxing and dehydration the sections were treated with 0·5% hydrogen peroxide in methanol for 30 min to block endogenous peroxidase, then rinsed in distilled water.

Sections for staining with anti-EMA (Clone E29, Dako Ltd, High Wycombe, Bucks) were placed in distilled water at 37°C for 10 min before immersing in 0·1% trypsin (Difco Laboratories, East Molesey, Surrey) in 0·1% calcium chloride (pH 7·8) for 20 min at 37°C. They were then washed in running tap water for 15 min, rinsed in phosphate-buffered saline (PBS) at pH 7·5 and twice washed in PBS containing 1% normal swine serum (NSS) for 5 min. They were then incubated with anti-EMA diluted 1 in 50 with PBS in a damp chamber for 1 h.

The procedure was then as follows: wash twice in PBS/NSS, incubate with rabbit anti-mouse immunoglobulins (Dako) diluted 1 in 40 with PBS for 30 min, wash twice in PBS/NSS, incubate with swine anti-rabbit immunoglobulins (Dako) diluted 1 in 40 with PBS for 30 min, wash twice in PBS/NSS, then incubate with peroxidase-anti-peroxidase (PAP) rabbit antiserum (Dako) diluted 1 in 40 in PBS for 30 min, wash twice in PBS/NSS followed by PBS rinse and incubation with diaminobenzidine (DAB)-hydrogen peroxide solution in PBS for 8 min. Then wash in distilled water, counterstain with Meyer's haematoxylin for 1·5 min, blue in tap water, dehydrate and mount.

AGF 4:48 hybridoma culture supernatant was obtained from the Department of Immunology, University of Birmingham. This antibody was raised against the human promyeloid cell line HL60 (Howie *et al.* 1984; Howie & Brown 1985). Sections for staining were rinsed in PBS, washed in PBS/NSS for 5 min (twice) and incubated in AGF 4:48 supernatant, diluted 1 in 3 with PBS in a damp chamber for 1·5 h.

The procedure was then the same as for the anti-EMA stained sections, except that after incubation with rabbit anti-mouse immunoglobulins, the sections were incubated with rabbit anti-mouse immunoglobulins peroxidase conjugated (Dako), diluted 1 in 40 in PBS for 30 min, preceded and followed by PBS washes. In preliminary experiments we found this enhanced the initial staining.

Controls were the omission of the primary antiserum in each case.

Lectin histochemistry

Sections prepared in the same way as for the anti-EMA staining were incubated in 0·001 mg/ml peroxidase-conjugated UEA-1 (E-Y Laboratories, Inc., San Mateo, CA, USA) for 24 h at 4°C. They were then washed in PBS for 5 min (twice), incubated in DAB-hydrogen peroxidase solution, counterstained with Mayer's haematoxylin and mounted as before.

Controls were the incubation of sections with UEA-1 peroxidase absorbed with 0·2 M fucose and the omission of the primary reagent.

Assessment

The staining patterns of both antibodies and UEA-1 were assessed for both intensity and consistency, consistency being defined on the basis of whether staining was distributed focally or uniformly throughout the tumour. Each variable was graded on an arbitrary scale of 0–3 by one author (M.G.B.): 0=negative staining, and 3=most intense or consistent staining. The two gradings were then summated to give a score of 0–6 for each section. The scored sections were classified into two groups: 0–3=negative–weakly positive, and 4–6=strongly positive.

These gradings were then related to histological type, differentiation, clinical stage at presentation and patient survival.

Histology

Haematoxylin and eosin stained sections were examined, together with Diastase-PAS stains where indicated. They were typed as serous, mucinous, endometrioid, clear-cell and undifferentiated according to the WHO classification (Serov *et al.* 1973). For the purposes of the study, the clear-cell and endometrioid carcinomas were grouped together. The numbers of tumours studied in each subtype is shown in Table 1.

Differentiation was graded on a I–III scale using similar criteria to those in previous studies (Pemberton 1940; Allen & Hertig 1949; Sorbe *et al.* 1982). The typing and grading of the tumours were performed by one author (T.P.R.).

Clinical information

Survival and follow-up data were available for all cases. Clinical staging at presentation was assessed using the FIGO system (Kottmeier 1976).

Statistical analysis

The statistical significance of the association between staining and tumour type, differentiation and clinical stage were investigated using Fisher's exact test (two-tail) and when appropriate Kendall's Tau-test. Survival curves were drawn using the method described by Kaplan & Meier (1958) and the differences between groups tested using the log rank test (Peto *et al.* 1977). For the purposes of these analyses, staining was subdivided into weak (i.e. negative and weakly positive groups) and strong; histological type into mucinous and non-mucinous; differentiation into well and moderate–poor groups; and stage into early (FIGO stage I/II) and advanced (FIGO stage III/IV).

Results

Patterns of staining. Positive staining with anti-EMA and UEA-1 occurred predominantly on cell membranes. This was seen either peripherally or on the free (luminal) surfaces of cells in tumours showing papillary, tubulo-acinar or intracystic growth patterns (Figs 1 & 2). Patchy or diffuse cytoplasmic staining was also seen in the same specimens in association with the cell surface staining, but it was variable and less intense. In contrast to anti-EMA, staining with AGF 4:48 was of the diffuse cytoplasmic type only (Fig. 3). With mucinous tumuors both anti-

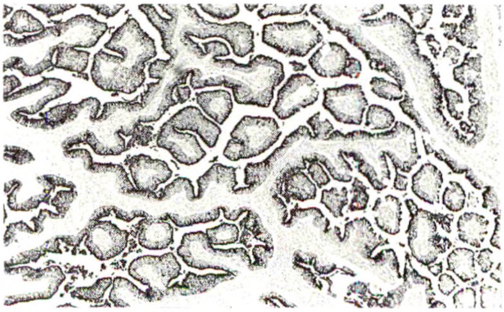

Fig. 1. Anti-EMA staining of a section from a Grade I mucinous adenocarcinoma showing peripheral pattern of localization. ×31.

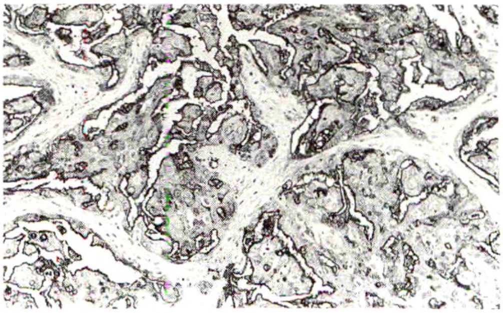

Fig. 2. UEA-1 staining of a section from a Grade II serous adenocarcinoma showing peripheral pattern of localization. ×80.

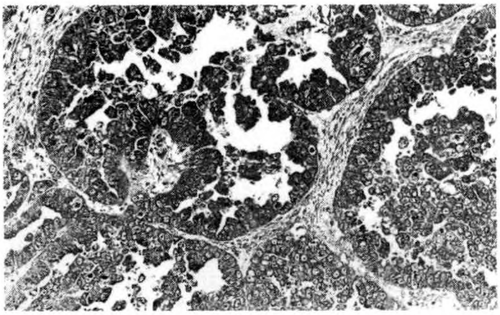

Fig. 3. AGF 4:48 staining of a section from a Grade II serous adenocarcinoma showing diffuse pattern of localization. ×80.

EMA and UEA-1 showed positive staining of extracellular mucin as well as tumour cells, but this was not seen with AGF 4:48. Individually each antibody and UEA-1 showed positive staining in most tumours. In those classed as weakly positive, staining was generally less intense and more patchy in distribution but patterns of uniform weak staining and intense but patchy staining were also seen.

Histological type (Table 1). Anti-EMA showed significantly stronger staining in non-mucinous tumours (Fisher's exact test (two-tail) $P=0{\cdot}002$; Kendall's Tau value=0·36). However, the only tumour with no staining was a clear cell tumour. Staining with AGF 4:48 and UEA-1 was more variable, with a large number of tumours being weakly positive or negative.

Histological differentiation (Table 2). There was no significant association between anti-EMA, AGF 4:48 and UEA-1 staining and histological grade.

Clinical stage (Table 3). Most patients had clinically advanced (FIGO stage III–IV) disease at presentation. No association was found between clinical stage and staining for both antibodies and UEA-1.

Survival. This is shown in Table 4. All patients underwent laparotomy followed by either high-dose single agent or combination cis-platinum chemotherapy. The overall median survival for the group was 15·7 months (95% confidence intervals 12·5 to 18·9 months). Of the 36 patients, 25 are dead at the time of writing and 11 are surviving with follow-up intervals ranging from 5 to 48 months. No association between staining for AGF 4:48, anti-EMA and UEA-1 and prognosis was observed.

Discussion

This study has demonstrated that ovarian carcinomata show wide variations in their staining with anti-EMA, AGF 4:48 and UEA-1, but with these small numbers we have been unable to

Table 1. The relation between histological type of ovarian carcinoma and the staining grade of anti-EMA, AGF 4:48 and UEA-1

Staining grade	Histological type: Mucinous ($n=9$)	Non-mucinous ($n=27$)	P*	τ†
Anti-EMA				
0–3	5	1	0·002	0·36
4–6	4	26		
AGF 4:48				
0–3	1	9	0·39	0·05
4–6	8	18		
UEA-1				
0–3	2	8	1·0	0·005
4–6	7	19		

* Fisher's test.

† Kendall's tau value.

Table 2. The relation between histological differentiation of ovarian carcinoma and the staining grade of anti-EMA, AGF 4:48 and UEA-1

Staining grade	Histological grade: Well ($n=21$)	Moderate/ poor ($n=15$)	P*	τ†
Anti-EMA				
0–3	4	2	1·0	0·006
4–6	17	13		
AGF 4:48				
0–3	5	5	0·71	0·01
4–6	16	10		
UEA-1				
0–3	4	6	0·26	0·05
4–6	17	9		

* Fisher's test.

† Kendall's tau value.

Table 3. The relation between FIGO stage at presentation of patients with ovarian carcinoma and the staining grade of anti-EMA, AGF 4:48 and UEA-1

Staining grade	FIGO stage I/II (n=7)	FIGO stage III/IV (n=29)	P*	τ†
Anti-EMA				
0–3	1	5	1·0	0·001
4–6	6	24		
AGF 4:48				
0–3	2	8	1·0	>0·001
4–6	5	21		
UEA-1				
0–3	0	10	0·15	0·09
4–6	7	19		

* Fisher's test.

† Kendall's tau value.

demonstrate any prognostic significance for these characteristics. The most obvious finding was the lack of anti-EMA positivity in mucinous tumours. The otherwise negative findings may be accounted for by the relatively small numbers studied with few tumours in each individual category: studies of larger numbers are needed before any firm conclusions can be drawn.

Malignant cells have been found to show alterations in the carbohydrate components of glycoproteins and glycolipids when compared with benign cells (Warren & Buck 1980; Hakoman 1975), which may affect the control of cell growth and proliferation. UEA-1 binds specifically to L-fucose (Walker 1984), which is a common component of *O*- and *N*-linked glycoconjugates (Beyer *et al.* 1979). This lectin and AGF 4:48 have been used in this study because changes in fucosylation have been associated with tumorigenicity and metastatic capacity in murine mammary tumours (Richards *et al.* 1981; Steiner *et al.* 1983; Dennis & Kerbel 1981). In studies on human breast carcinoma (Walker & Day 1986; Walker 1984) an association was found between AGF 4:48 staining and tumour differentiation. On the other hand, no association was found between UEA-1 and tumour differentiation although loss of UEA-1 binding was seen in tumours with axillary node metastases. In our series there was no association between immunostaining and differentiation.

The expression of epitopes recognized by monoclonal antibodies to EMA have been found to show considerable heterogeneity covering a wide range of molecular weights (Cordell *et al.* 1985; Turnbull *et al.* 1986). EMA is composed of a group of high-weight glycoproteins (Ormerod *et al.* 1983). The anti-EMA antibody used in this study has been shown to react with material in the molecular weight range 265–400 kDa (Cordell *et al.* 1985). This compares with 30–450 kDa for HMFG-1 and 90–450 for HMFG-2 (Turnbull *et al.* 1986). This diversity of expression might be expected to produce different patterns of staining in tumours that could have prognostic value but we have been unable to demonstrate this in ovarian carcinoma. Investigations carried out on breast carcinomas using HMFG-1 and HMFG-2 have produced conflicting results. Berry *et al.* (1985) found no association between staining and various prog-

Table 4. The relation between survival of patients with ovarian carcinoma and the staining grade of anti-EMA, AGF 4:48 and UEA-1

Staining grade	No. patients (n=36)	No. deaths (n=25)	Survival (months) Median	Survival (months) (95% CI)	χ^2	P
Anti-EMA						
0–3	6	3	13·7	*	1·67	0·20
4–6	30	22	15·7	(12·8 to 18·6)		
AGF 4:48						
0–3	10	8	10·2	(6·5 to 14·0)	3·21	0·07
4–6	26	17	20·7	(8·8 to 32·3)		
UEA-1						
0–3	10	8	13·7	(8·2 to 19·2)	0·75	0·39
4–6	26	17	16·0	(7·3 to 24·7)		

* Cannot be calculated.

nostic indices, but Wilkinson *et al.* (1984) reported that negative HMFG-1 staining of tumours carried a poor prognosis. These discrepancies may be due to the small number of cases studied or the methods of grading the staining patterns.

In grading positive anti-EMA binding in our study we have not distinguished between cell surface and cytoplasmic staining for the purposes of simplicity. However, Wilkinson *et al.* (1984) found no association between cytoplasmic or cell surface staining and patient prognosis in studies with HMFG-1 and HMFG-2 on breast carcinomas. It is therefore unlikely that these antibodies will be useful in determining tumour differentiation or prognosis.

In conclusion the results of this study show that whilst ovarian carcinomas show variations in their staining reactions to anti-EMA, AGF 4:48 and UEA-1, these are not helpful in determining prognosis in individual cases.

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A protocol for the routine measurement of lactate and pyruvate in cord blood

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Summary. The influence of the site of sampling and the delay in sample collection on cord blood concentrations of lactate and pyruvate were investigated. A delay in sample collection of >1 min after cord clamping could invalidate the results obtained. Samples from umbilical artery had higher lactate values (mean 3·13 mmol/l) than paired vein samples (mean 2·32 mmol/l) but there were no significant differences in lactate values between different sites sampled within the umbilical vein. A calculation was devised to circumvent the need to take cord blood samples immediately after delivery.

Current methods of assessing the well-being of the newborn, such as Apgar score (Apgar 1953) and measurement of cord blood gases (Sykes *et al.* 1982) may be less than ideal, reflecting only the status of the newborn at the time of measurement. Even full blood gas analysis may give only an incomplete picture of recent metabolic state. Neither method gives any indication of the levels of hypoxia to which the fetus may have been exposed during labour (Lancet 1982).

Lactic acid is the ultimate endpoint of anaerobic glycolysis, and can be made only from, and converted to, pyruvic acid; this interconversion depends on the enzyme lactate dehydrogenase. The ratio of lactate to pyruvate may vary and can reflect the cellular redox state; in conditions of cellular hypoxia, reduced moieties increase and correspondingly the ratio of extracellular lactate to pyruvate is increased (Huckabee 1958). The lactate to pyruvate ratio has been used to differentiate between increases in lactate due to hypoxia and those due to other causes (Low *et al.* 1974). Therefore, in addition to current methods, assessment of fetal hypoxia might be augmented by the measurement of lactic acid, either alone or preferably in conjunction with pyruvic acid. Measuring the metabolic component of any acidosis gives an additional indication of the tissue oxygen debt in the newborn (Low *et al.* 1974).

Numerous workers have used lactate measurement, with or without pyruvate, either as a measure of fetal status at birth (Derom 1964; Low *et al.* 1974, 1975; Ditesheim & Bossart 1979; Smith *et al.* 1983; Suidan & Young 1984; Katz *et al.* 1987) or to assess the effect of maternal intravenous infusion (Ramanathan *et al.* 1984; Evans *et al.* 1986). Although those who have specified manner and timing of collection have indicated that time is critical, there is no published work defining acceptable time limits within which samples for the measurement of lactate and pyruvate can be collected. Two potential causes of delay may invalidate results. First, when plasma samples are to be assayed (Ditesheim & Bossart 1979) there are inevitable delays caused by centrifugation, as may have occurred in the work of Evans *et al.* (1986)

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Second, changes in levels may occur if metabolism continues after sampling. For example, Low *et al.* (1974, 1975) noted that protein precipitation to halt further metabolism 'was carried out within 3 minutes of sampling' but they did not specify whether there was an additional delay between delivery and sampling, and, even more imprecise, Katz *et al.* (1987) reported that samples were 'sent to the metabolic laboratory (a distance of 150 m)' without specifying whether the specimen had been deproteinated first.

We have therefore examined the effects of delay on the values obtained and established a protocol for the collection of such specimens, appropriate for routine use in a busy labour ward.

Subjects and methods

A total of 30 infants was studied and three experiments were performed; no formal estimations of required sample size were made as no data existed upon which to base such estimations. Double clamped segments of umbilical cord were obtained immediately after birth in 10 infants. In one the cord was clamped before birth and in the remainder within 1 min of birth before the infant had made its first respiratory effort. The time of cord clamping was designated as 0 min. The cords were kept at room temperature and 2-ml blood samples were withdrawn from the umbilical vein at 1, 2, 3, 4, 5, 10, 15 and 20 min after clamping. Each blood sample was immediately placed in a weighed tube containing 5 ml of chilled perchloric acid and stored at −20°C. All specimens were analysed for lactate and pyruvate by a modification of the fluorimetric method of Lloyd *et al.* (1978). In 12 other infants simultaneous samples were drawn from the umbilical artery and vein, and in a further eight infants simultaneous samples were drawn from the umbilical vein (a) as close to the fetus as possible and (b) as close to the placenta as possible. All of these samples were taken within 1 min of cord clamping

It was initially planned to analyse the data from the time series by an analysis of variance. The fluctuation of values between 1 and 10 min resulted in abandoning this approach (see results section for details). For comparison of arterial and venous sampling and for varying the site of sampling in the umbilical vein, the ratio of the data pairs was calculated. This ratio was log transformed and the 95% range of the ratios was calculated.

Results

Temporal changes in whole blood lactate and pyruvate concentrations in 10 umbilical cords are shown in Table 1. There were marked fluctuations in some patients in the levels measured between 1 and 10 min after cord clamping. Thereafter, however, a consistent trend of progressively rising lactate and falling pyruvate values became apparent. The lactate to pyruvate ratio (Table 1) rose, in general, over all the time-points and showed less variation than was noted for lactate and pyruvate levels during the first 10 min, suggesting that lactate and pyruvate levels changed in parallel.

The trends were quantified by estimating the rate of change of both moieties by two methods: (i) by measuring the gradient of the line best fitting the 5-, 10-, 15- and 20-min time-points for each patient and then calculating the mean gradient; (ii) by calculating the mean change between the 1- and 10-min time-points and hence the rate of change (gradient). For lactate the gradients were 18 and 30 and for pyruvate −1·05 and −1·1. As these were approximations it was decided, on an arbitrary basis, to calculate from the 20-min values what the '0'-min values would be if lactate levels increased at 20 μmol/l/min and pyruvate levels decreased at 1 μmol/l/min. The corrected 20-min values are plotted against the 1-min values in Figs 1a and b. These corrected values provide a close estimate to the 1-min values and potentially provide an alternative means of obtaining a measure of lactate and pyruvate levels at birth.

In the paired samples, artery blood lactate values were consistently higher than the vein blood values (Fig. 2a). The mean ratio of arterial to venous lactate was 1·36 (95% range of the ratio 0·85–2·17) Figure 2b shows that there was no apparent difference in pyruvate levels between umbilical artery and vein (mean ratio 1·11, 95% range of the ratio 0·76–1·63) although again the umbilical artery value tended to be the higher. Similarly the site of sampling from the umbilical vein did not appear to affect the values obtained in eight infants (Table 2) (mean ratio for lactate 0·97, 95% range 0·89–1·06, mean ratio for pyruvate 0·98, 95% range 0·88–1·10).

Table 1. Temporal changes in whole vein blood lactate and pyruvate concentrations in 10 umbilical cords

	Infant	Minutes after cord clamping									
	no	1	2	3	4	5	10	15	20	Mean	(SD)
Lactate (µmol/l)	1	3045	3028	3076	3321	3132	3250	3329	3456	3205	(157)
	2	1053	1082	976	1310	1324	1469	1408	1568	1274	(214)
	3	3709	4078	3764	3712	3549	3686	3766	3841	3763	(152)
	4	1980	2014	2067	2010	2092	2216	2207	2321	2113	(122)
	5	2850	2958	2740	2909	2838	3183	3175	3190	2980	(179)
	6	1579	1797	1690	1716	1852	1926	2005	1962	1816	(148)
	7	3426	3222	3394	3569	3553	3655	3691	3660	3521	(162)
	8	1662	1871	1827	2184	1993	2074	2223	2274	2014	(215)
	9	4327	4361	4349	4435	4364	4526	4530	4769	4458	(149)
	10	1977	2099	2081	2080	2282	2307	2775	2699	2288	(299)
	Mean	2561	2651	2596	2725	2698	2829	2911	2974		
	(SD)	(1066)	(1056)	(1049)	(1013)	(947)	(971)	(959)	(984)		
Pyruvate (µmol/l)	1	168	174	151	174	167	159	156	161	163·8	(8·4)
	2	72	76	68	71	73	74	65	72	71·4	(3·5)
	3	205	199	206	201	205	196	193	183	198·5	(7·8)
	4	114	110	110	107	103	103	95	87	103·6	(8·9)
	5	171	170	168	165	165	155	150	142	160·8	(10·6)
	6	102	110	99	98	106	101	97	90	100·4	(6 0)
	7	173	157	156	159	171	158	140	137	156·4	(12·8)
	8	101	110	105	106	105	100	104	99	103·8	(3·6)
	9	206	191	198	195	195	178	179	173	189·4	(11·5)
	10	144	143	138	136	146	130	128	132	137·1	(6·8)
	Mean	145·6	144·0	139·9	141·2	143·6	135·4	130·7	127·6		
	(SD)	(46·4)	(40·9)	(44·6)	(44·3)	(44·4)	(39·8)	(40·5)	(38·8)		
Lactate/pyruvate ratio	1	18 1	17·4	20·4	19·1	18·8	20·4	21·3	21·5	19·62	(1·50)
	2	14·6	14·2	14·4	18·5	18·1	19·9	21 7	21·8	17·89	(3·18)
	3	18·1	20·5	18·3	18·5	17·3	18·8	19·5	21·0	18·99	(1·25)
	4	17·4	18·3	18·8	18·8	20·3	21·5	23·2	26·7	20·62	(3·09)
	5	16·7	17·4	16·3	17·6	17·2	20·5	21·2	22·5	18 67	(2·36)
	6	15·5	16·3	17·1	17·5	17·5	19·1	20·7	21·8	18·18	(2·17)
	7	19·8	20·5	21·8	22·4	20·8	23·1	26·4	26·7	22·69	(2·61)
	8	16·5	17·0	17·4	20·6	19·0	20·7	21·4	23·0	19·44	(2 34)
	9	21·0	22·8	22·0	22·7	22·4	25·4	25·3	27·6	23·65	(2·21)
	10	13·7	14·7	15·1	15·3	15·6	17·7	21·7	20·4	16·79	(2·89)
	Mean	17·14	17·92	18·14	19·10	18·70	20·73	22 23	23·29		
	(SD)	(2·25)	(2·70)	(2·63)	(2·26)	(2·01)	(2·22)	(2·13)	(2·66)		

Discussion

The main practical problem associated with measuring intermediate metabolites such as lactic and pyruvic acid is that continuing metabolism within a sample alters levels. Therefore, it is necessary to halt that metabolism immediately, e.g. by adding the sample to chilled perchloric acid. Also, in the labour ward there is a potential delay between delivery/cord clamping and sampling.

The marked fluctuations in both lactate and pyruvate in the first 5 min after cord clamping noted in some of our patients makes any delay inappropriate, a value obtained from a sample collected within 1–5 min would, potentially, be of doubtful significance. Later lactate levels show a steady rise and pyruvate a steady fall; despite the initial fluctuations this is the underlying trend. This pattern is consistent and could be explained as follows. Initially metabolism, via both aerobic and anaerobic pathways, continues unaffected by cord clamping in the non-red cell components. As oxygen supplies are used up aerobic metabolism diminishes and anaerobic metabolism becomes dominant, leading to rising

Table 2. The effect of sampling site on umbilical vein blood lactate and pyruvate concentrations

Infant no.	Whole blood lactate (μmol/l) Fetal site	Placental site	Ratio*	Whole blood pyruvate (μmol/l) Fetal site	Placental site	Ratio*
23	1079	1089	0·99	83	84	0·99
24	3640	3700	0·98	178	190	0·94
25	2458	2718	0·90	171	183	0·93
26	1253	1237	1·01	70	69	1·01
27	1110	1184	0·94	82	80	1·02
28	3221	3203	1·01	207	203	1·02
29	1029	1043	0·99	94	91	1·03
30	2952	3128	0·94	155	168	0·92

* Fetal to placental concentration ratio.

lactate levels and a higher lactate:pyruvate ratio. An element of this variation might be due to assay imprecision. The within-batch precision for this automated method for routine lactate/pyruvate analysis is <5%. All assays for a given patient were done on a single assay run to abolish between-batch variation. On the basis of our results it seems realistic to suggest that a sample has to be taken within 1 min of cord clamping to be reliable. Under normal circumstances on a busy labour ward this is probably not possible and whilst this might not matter when measuring the individual metabolites the delay is significant when the ratio is to be considered because lactate increases and pyruvate decreases and consequently the ratio rises. A value obtained after a delay of ≥10 min can be corrected by calculating the levels of lactate and pyruvate at time of birth, as the underlying trends are consistent, and then calculating a more meaningful ratio.

The effect of varying the sampling site seems less important. We have endeavoured in our method of analysis to highlight those circumstances where an observed difference might be due to an actual difference rather than assay imprecision. Where the ratio between two sites is significantly greater or less than 1 then it is likely that the difference is not due to assay imprecision and chance variation alone. It is important therefore to be aware of the potential differences between the two umbilical vessels: both lactate and lactate: pyruvate ratios were higher in the deoxygenated blood of the umbilical artery. Passage of fetal blood through the placental circulation results in a clearance of lactate and a shift towards the oxidized state of the lactate dehydrogenase enzyme system. The extent of this clearance varies between individuals as indicated by the range of ratios of arterial:venous lactate. Factors which might

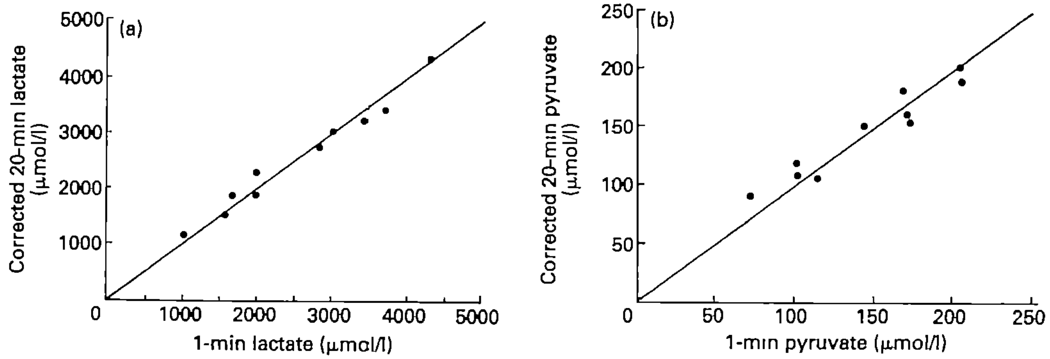

Fig.1. (a) Corrected 20-min lactate levels against measured 1-min lactate levels in umbilical vein blood. (b) Corrected 20-min pyruvate levels against measured 1-min pyruvate levels in umbilical vein blood.

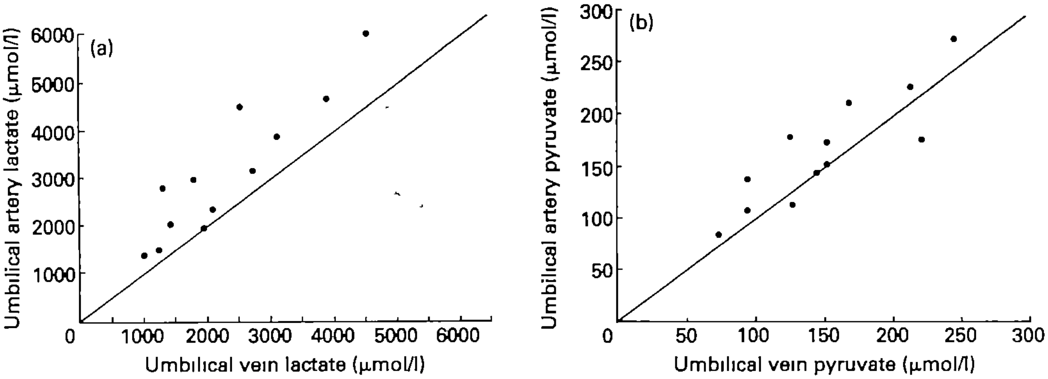

Fig.2. (a) Lactate concentrations in 12 paired umbilical vein and artery blood samples. (b) Pyruvate concentrations in 12 paired umbilical vein and artery blood samples

influence this transfer include fetal and maternal lactate levels and placental function; this is an important, albeit poorly understood, area and warrants further investigation. Although the umbilical artery level is probably more representative of the fetus, the umbilical vein is much easier to sample and we suggest it be used as the site for routine sampling. The small differences observed in our samples from separate sites in the umbilical vein are not significant and are probably due to assay imprecision. When sampling from the umbilical vein it must be ensured that a sample is not inadvertently taken from the umbilical artery.

Earlier reports of cord blood lactate measurements have emphasized the need for urgency in the collection of samples but unfortunately in some reports the sampling protocol casts doubt on the validity of the measurements. The practices adopted by Derom (1964) and Suidan & Young (1984) would comply with the suggestions made here. We have not examined the effect of delay in centrifuging samples to obtain plasma. Although cord blood was collected immediately after delivery by Ditesheim & Bossart (1979) the inevitable delay associated with centrifugation may cast doubt on some of their results. Similarly Evans *et al.* (1986) state that separation of plasma from their samples, collected at time of delivery, was achieved within 5 min of collection.

Delay in the collection of specimens for lactate and pyruvate estimation can obviously affect the results obtained. The measurement of lactate, with or without pyruvate, is another potentially valuable tool in the assessment of fetal status at birth, as a measure of the degree of intrapartum hypoxia and to assess the effect of various forms of intrapartum management, such as intravenous infusion and prolongation of the second stage, on the fetus. The value of lactate and pyruvate measurements should not be diminished by the careless collection of specimens.

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Antiserum to pregnancy-associated plasma protein A (PAPP-A) recognizes human haptoglobin

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Summary. The presence of pregnancy-associated plasma protein A (PAPP-A) in non-pregnancy serum has been questioned with reference to insufficient specificity of the antibodies raised against this glycoprotein in some departments and used in immunoassay. For convenience, but also because of this unclear situation, many laboratories now use the only commercially available anti-PAPP-A preparations in their assays. By analysing pregnancy and non-pregnancy serum with two-dimensional electrophoresis (2-DE) and Western blotting, we could demonstrate that this antiserum marketed by Dakopatts (Denmark) was capable of binding haptoglobin whereas our own (Dr P. Bischof) antibody preparation did not recognize haptoglobin.

Pregnancy-associated plasma protein A (PAPP-A), a large glycoprotein, was described and isolated by Lin *et al.* (1974). Its concentration in the maternal circulation increases throughout pregnancy. Measurement of serum PAPP-A concentrations can have diagnostic value in pathological situations such as ectopic pregnancy where PAPP-A levels are very low (or undetectable) although levels of chorionic gonadotrophin (hCG) are not affected (Sinosich *et al.* 1985). In pre-eclampsia, serum PAPP-A is raised, even before the onset of symptoms. A role in the causal development of this disease (rather than a consequence) has therefore been proposed, and the protein has gained increased interest (Toop & Klopper 1981).

It is accepted that the major source of PAPP-A in pregnancy is the syncytiotrophoblast, but the protein has also been found in other body fluids and Bischof *et al.* (1984) reported its synthesis by human decidualized endometrium. This result and the reported presence of PAPP-A in non-pregnancy serum (Bischof *et al.* 1981; Bersinger & Klopper 1984) have been controversial subjects for a long time.

Various immunoassay methods are available for estimating PAPP-A. The only commercially available anti-PAPP-A preparation, the polyclonal rabbit antiserum marketed by Dakopatts (Denmark), is used by many laboratories, either exclusively or in combination with laboratory-made polyclonal rabbit antibodies. These have been criticized as being of insufficient specificity and responsible for the 'detection' of PAPP-A in the above-mentioned reports. In this study we investigate whether the Dakopatts anti-PAPP-A antiserum (which some groups recommend in order to avoid problems of specificity) would indeed be devoid of any antibodies reacting towards serum proteins other than PAPP-A.

Materials and methods

Serum samples from pregnant and non-pregnant women as well as from healthy men were stored at −20°C without a preservative before 2D-electrophoresis as described by O'Farrell (1975). Reduced and denatured serum proteins (100 μg) or pure haptoglobin (Sigma Co., St Louis, USA; 10 μg) were first separated for 10 500 V-h on 1·5×14 mm rod isoelectrofocusing gels containing 2·5% (v/v) ampholytes (LKB, Sweden) at a pH range of 3·5–10·0. The rods were then placed on top of 11% T, 2·5% C gels

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(180×160×1·5 mm) for electrophoresis in the second dimension. The protein patterns were revealed with a modified silver diamine staining procedure (Wiederkehr *et al.* 1985). Electroblotting ('Western blotting') was done as described by Towbin *et al.* (1979) in a Trans-blot cell (Bio-Rad, Richmond, CA, USA) at 60 V for 3 h. After transfer the nitrocellulose papers (LS-45, Schleicher & Schuell, Switzerland) were blocked with Tween-20 (0·3% v/v) in Tris-buffered saline, pH 7·5 (TBS). We used the Immun-blot (GAR-HRP) assay kit from Bio-Rad and followed the manufacturer's instructions. The first antibody (rabbit anti-PAPP-A, batch 11, or anti-human haptoglobin from Dakopatts, or anti-PAPP-A prepared and kindly donated by Dr P. Bischof, Geneva) was diluted 1:500 with TBS-0·3% Tween. The second antibody (HRP-conjugated goat anti-rabbit IgG from Bio-Rad) was diluted 1:1000 with the same buffer. The peroxidase (HRP) reaction was then demonstrated with 4-chloro-1-naphthol and hydrogen peroxide in TBS as described in the kit's manual.

Human haptoglobin (Calbiochem, Lucerne, Switzerland; 4 mg) was incubated with CNBr-activated Sepharose (0·4 g) according to the manufacturer's instructions (Pharmacia, Sweden); 3·4 mg were coupled to the gel. Then the Dakopatts anti-PAPP-A was filtered through this negative affinity column and the eluent was tested in the Western blotting procedure as above.

Results

When pooled late pregnancy serum (PLPS) was analysed on 2D-electrophoresis and the blot developed with the rabbit anti-PAPP-A immunoglobulin from Dakopatts (batch 11), the typical pattern for human haptoglobin with the two subunits α (15 kD) and β (43 kD) was obtained (Fig. 1A). The same picture was found with female non-pregnancy serum (Fig. 1B) and with male serum (not shown). Pure haptoglobin, when treated in the same way, yielded a positive reaction for the β subunit with the same antiserum; the α subunit was not detected (Fig. 1C).

When the antiserum to PAPP-A was filtered through a haptoglobin-Sepharose column, the filtrate, tested against PLPS, and at the same final dilution, as described for Fig. 1A, gave only a very faint coloration which could not be reproduced photographically.

When the same PLPS was analysed with anti-haptoglobin the same pattern as with anti-PAPP-A was obtained (Dakopatts antisera) (Fig. 2). The rabbit anti-PAPP-A antiserum prepared in Geneva by Dr P. Bischof gave no reaction with either pure haptoglobin or PLPS (not illustrated).

Discussion

The results show that the polyclonal rabbit antiserum marketed by Dakopatts contains antibodies which react against human hap-

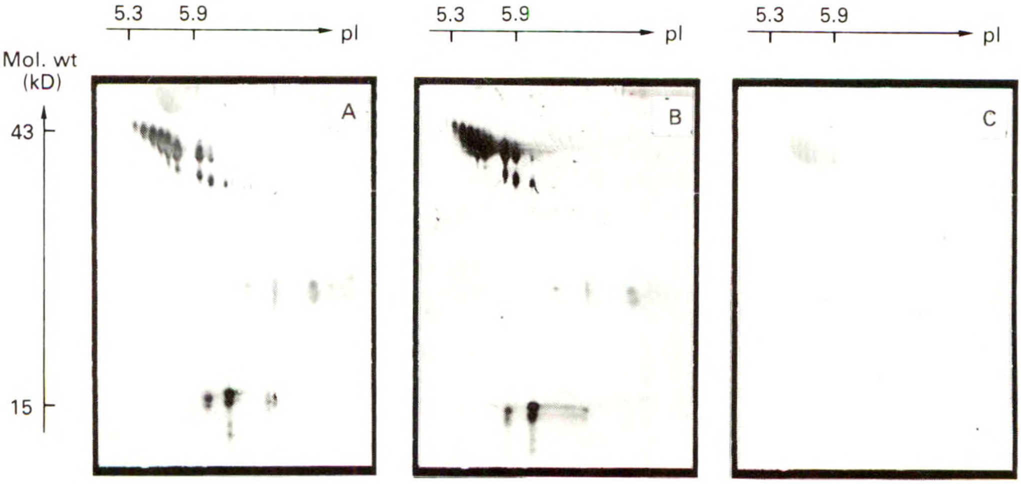

Fig. 1. Western blots of human sera or haptoglobin analysed on two-dimensional electrophoresis (2-DE) and developed with anti-PAPP-A antiserum (Dakopatts, Denmark): (A) pooled late pregnancy serum; (B) female non-pregnancy serum; (C) human haptoglobin.

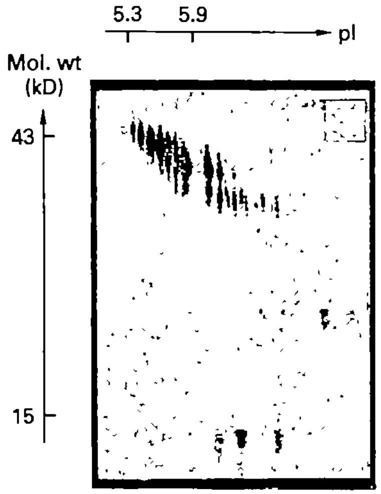

Fig. 2. Western blot of pooled late pregnancy serum analysed on 2-DE and developed with antiserum against human haptoglobin.

toglobin, an antigen present in the serum of pregnant as well as non-pregnant individuals. We do not know whether PAPP-A has common antigenic determinants with haptoglobin. The observation that the anti-PAPP-A preparation from Geneva, also a polyclonal rabbit antiserum, did not recognize haptoglobin under identical conditions (antibody titre and dilution), rather suggests that the populations of antibodies directed against PAPP-A and haptoglobin are independent. Binding to PAPP-A itself could not be demonstrated with this method since the denatured antigen is not recognized by either antiserum against PAPP-A. All antisera tested here have a high affinity towards PAPP-A; the aim of this study, however, was to demonstrate that the Dakopatts antiserum was also binding a serum protein of smaller size (and in spite of denaturation). This is further illustrated by the results obtained after negative affinity chromatography.

Whether the occasional reports of finding PAPP-A in non-pregnancy sera (Bischof *et al.* 1981; Bersinger & Klopper 1984) are indeed due to haptoglobin remains to be proven. We would, however, suggest that any result obtained from assays using non-treated Dakopatts antiserum against PAPP-A be interpreted with caution. Many laboratories (including our own) are currently using this antiserum preparation in ELISA, or in other immunometric methods involving excess labelled antibody and therefore particularly prone to interference by anti-haptoglobin antibodies. In tests using labelled antigen (i.e. RIA) there would be no such interference as long as the anti-PAPP-A and the anti-haptoglobin immunoglobulins are separated from each other as suggested above.

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Immunological heterogeneity of pregnancy-associated plasma protein-A (PAPP-A). Effects on the radioimmunoassay of PAPP-A

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Summary. Pregnancy-associated plasma protein-A (PAPP-A) is a macromolecular glycoprotein produced by the trophoblast during pregnancy. Because the presence of PAPP-A in non-pregnant females is controversial, we re-evaluated our own radioimmunoassay technique for PAPP-A in the light of new observations about its immunological heterogeneity. Irrespective of the antibody (Geneva anti-PAPP-A or Dako anti-PAPP-A) the use of EDTA pregnancy plasma instead of pregnancy serum as a standard yielded different slopes of the standard curves and estimated significantly different amounts of PAPP-A in test samples. Moreover, highly purified tracers, isolated from maternal EDTA pregnancy plasma or pregnancy serum also produced significantly different results. So that the use of a tracer purified from EDTA plasma and EDTA pregnancy plasma as a standard will yield measurable levels of PAPP-A in non-pregnant female serum whereas the use of a tracer purified from maternal pregnancy serum and maternal pregnancy serum as a standard will not detect PAPP-A in the same samples. We conclude that, irrespective of the antiserum used, but depending on the biological origin of the tracer and the standard, different results will be obtained. PAPP-A is clearly immunologically heterogeneous, and the immunorecognition of PAPP-A will depend on whether or not blood coagulation has taken place.

The purification and partial characterization of pregnancy-associated plasma protein-A (PAPP-A) was first reported by Lin *et al.* (1974*a*). PAPP-A is a large homotetrameric glycoprotein (M_r=800 000) found in increasing concentration in maternal serum as pregnancy progresses. There is agreement that PAPP-A originates mainly from the trophoblast in pregnancy but its presence in the circulation of non-pregnant subjects is still controversial, probably because of the different assays and reagents used to measure PAPP-A. Chemnitz *et al.* (1986) questioned the specificity of some PAPP-A antisera. Since Lin *et al.* (1974*b*) described the antibody crossed immunoelectrophoretic technique for measuring PAPP-A, many different assays have been proposed: rocket immunoelectrophoresis (Bischof *et al.* 1979), radiorocket line immunoelectrophoresis (Folkersen *et al.* 1981), radioimmunoassays (Bischof *et al.* 1981; Sinosich *et al.* 1982;

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Anthony *et al.* 1983; Pinto-Furtado *et al.* 1984) and enzyme immunoassays (Bersinger 1983; Pledger & Belfield 1983; MacDonald *et al.* 1984). Only radioimmunoassays (RIA) and enzyme immunoassays (EIA) are sufficiently sensitive to detect low levels of PAPP-A. Using these methods some authors have found measurable levels of PAPP-A in non-pregnant subjects (Bischof *et al.* 1981; Bersinger & Klopper 1984) whereas others were unable to do so (Anthony *et al.* 1983; Sinosich *et al.* 1985; Pledger & Nicol 1983). Furthermore, using our RIA we measured low but detectable levels of PAPP-A in ectopic pregnancies (Bischof *et al.* 1983) whereas Grudzinskas *et al.* (1985) found most values to be below the sensitivity limit of their RIA. Since these differences were not due to differences in the sensitivity limits of the respective assays, we re-evaluate here our own RIA in the light of recent observations about the immunological heterogeneity of PAPP-A (Bischof & Meisser 1989).

Materials and methods

Antibodies

We tested two different antisera: Dako anti-PAPP-A, obtained from Dakopatts (Copenhagen, Denmark) and Geneva anti-PAPP-A (Ge) which was raised in rabbits against a semi-purified PAPP-A preparation. This antiserum was extensively adsorbed with serum from non-pregnant women. The Geneva anti-PAPP-A is the antiserum routinely used in our RIA.

Since the titre of the antisera is different, these were compared at dilutions giving the same binding (Dako 1:32 000, Ge 1:16 000).

Antigens

PAPP-A was purified from maternal late pregnancy serum (PAPP-A$_s$) and from maternal late pregnancy EDTA plasma (PAPP-A$_p$, 2 mg/ml ethylene diaminotetraacetate) by a modification of the method of Davey *et al.* (1983). Briefly, 100 to 150 ml of plasma or serum were dialysed against buffer A (0·05 mol/l phosphate buffer containing 0·1 mol/l NaCl, pH 7·4) and subjected to ion exchange chromatography on DEAE-Sepharose C16B (Pharmacia, Uppsala, Sweden). Bound proteins were eluted with a NaCl gradient (0·1–1·0 mol/l) in buffer A. The fractions containing immunoreactive PAPP-A (as measured by RIA) were dialysed, pooled and subjected to affinity chromatography on heparin-Sepharose C14B (Pharmacia, Uppsala, Sweden). Heparin-bound PAPP-A was eluted with a NaCl gradient (0·1–1·0 mol/l) in buffer A. PAPP-A containing fractions were pooled and concentrated on an Amicon XM100A membrane (Bender–Hobein, Basel, Switzerland) and subjected to molecular sieve chromatography on ultrogel ACA34 (1×60 cm, IBF, Villeneuve-la-Garenne, France). The preparation was eluted with buffer A. The fractions containing immunoreactive PAPP-A were concentrated, divided into aliquots, and stored at −20°C.

Radioiodination

Purified PAPP-A preparations were radiolabelled with ^{125}I using the lactoperoxidase technique as reported previously (Bischof *et al.* 1981). The iodination mixtures were applied to a Sepharose C14B column (1×60 cm, Pharmacia, Uppsala, Sweden) and eluted with buffer A. ^{125}I-PAPP-A was repurified on a Sephadex G200 column (1×60 cm, Pharmacia, Uppsala, Sweden) and eluted with buffer A. The fractions containing ^{125}I-PAPP-A were stored in aliquots at −20°C.

Repurification of ^{125}I-PAPP-A on Sephadex G200 was repeated for each frozen aliquot before being used as tracer in the RIA.

RIA

The RIA used in the present study has been described in detail previously (Bischof *et al.* 1981). The standard was either a calibrated pool of maternal late pregnancy EDTA plasma (called E. Stand thereafter: PAPP-A 120 μg/ml) or the International Reference preparation 78610 (called Stand 78610 thereafter: PAPP-A 100 iu/l) kindly supplied by Dr Sizaret (Bohn *et al.* 1980). Serial dilutions of these pools (1:100 to 1:6400, 11 points in duplicate) were used as standard curves. Analysis of results and standard curve used a Cyber 170 computer with the Riapro program written by V. B. Faden and D. Rodbard.

Electrophoresis and Western blotting

Polyacrylamide gradient gel electrophoresis was performed as described by Weber *et al.* (1972) on gradient gels (2–16% Pharmacia, Uppsala, Sweden) in the absence (non-denaturing conditions) of SDS. After electrophoresis the gels were either stained with silver nitrate or subjected to Western blotting. Electrotransfer on to nitrocellulose membranes (Biorad, Zürich, Switzerland) was performed at 12 V/4A for 10 h at 4°C in phosphate buffer (0·025 mol/l, pH 6·5). The nitrocellulose membrane was then incubated for 6 h in 0·5% gelatin in Tris-HCl buffer (0·01 mol/l containing 0·15 mol/l NaCl, pH 7·4), washed and incubated overnight with the anti-PAPP-A antisera (1:150 in Tris-HCl buffer). The nitrocellulose bound PAPP-A-anti-PAPP-A complex was then stained by a second antibody bound to peroxidase using chloronaphthol as a substrate.

Autoradiography

After polyacrylamide gradient gel electrophoresis, the gels were fixed for 1 h in a methanol-acetic acid-water solution (50/10/40) and rehydrated in water. The gels were then exposed to X-ray films (Typon RP-L, Typon, Burgdorf, Switzerland) in an appropriate cassette for different periods of time. After exposure the film was processed as for routine X-rays.

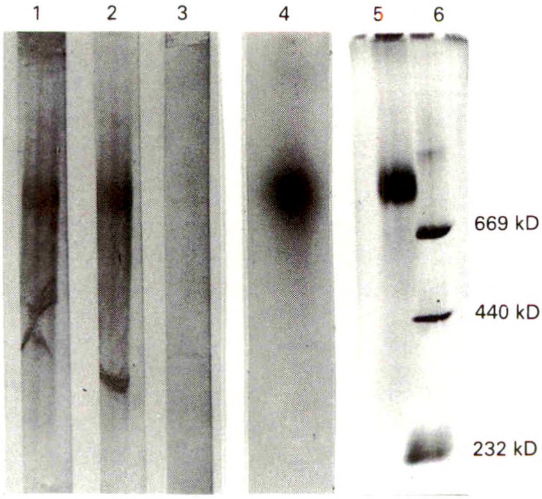

Fig. 1. PAPP-A purified from late pregnancy serum was subjected to electrophoresis on polyacrylamide gradient gel (2–16%) under non-denaturing conditions. (1) Immunoblotting with Dako anti-PAPP-A; (2) with Ge anti-PAPP-A; (3) with normal rabbit serum; (4) autoradiogram of the same preparation after radiolabelling with ^{125}I; (5) silver nitrate stain of PAPP-A preparation; and (6) standards.

Immunoadsorption

EDTA plasma and serum were obtained from healthy non-pregnant females and male volunteers. The samples were stored at −20°C. Aliquots of these were incubated under constant agitation for 2 h at room temperature either with Dako anti-PAPP-A or with unrelated antibodies (anti-haptoglobin, Behring, Zürich, Switzerland, and anti-C$_3$ Janssen, Amimed, Basel, Switzerland) bound to protein-A-Sepharose (Pharmacia, Uppsala, Sweden). After incubation, the samples were centrifuged at 5000 ***g*** for 15 min and the supernatants stored at −20°C.

Results

The purity of the PAPP-A preparations has been evaluated by polyacrylamide gradient gel electrophoresis (PAGGE) under non-denaturing conditions, by autoradiography and by Western blotting (Fig. 1). One unique band at 800 000 daltons was observed on polyacrylamide gels and on the autoradiogram. This unique band was immunodetected by both anti-PAPP-A antibodies used. Using these techniques, no contaminant could be detected. Considering the sensitivity limits of these techniques, one can assume that the PAPP-A preparations were 99% pure.

Irrespective of the antiserum and the nature of the standard used (E. Stand or Stand 78610) the slope of the standard curves was significantly ($P<0{\cdot}03$) flatter when the tracer used in the RIA was purified from maternal serum (^{125}I–PAPP-A$_s$) than from maternal EDTA plasma (^{125}I-PAPP-A$_p$) (Table 1). Irrespective of the antiserum and the origin of the tracer, Stand 78610 generated significantly ($P<0{\cdot}005$ to $<0{\cdot}0005$) flatter standard curves than E. Stand (Table 1). Furthermore, the slope of the displacement curves obtained with a highly purified preparation of PAPP-A$_p$ was significantly steeper ($P<0{\cdot}03$) than with PAPP-A$_s$ (Table 1). However, the PAPP-A$_p$ preparation gave a displacement curve which was parallel to maternal EDTA plasma, and the PAPP-A$_s$ preparation gave a curve parallel to maternal serum. Providing the same tracer and the same standards were used, the two different anti-PAPP-A antisera

Table 1. Effects of different variables on the slope (logit B/Bo *vs* log dose) of the standard curve

		Tracers					
		^{125}I-PAPP-A$_p$			^{125}I-PAPP-A$_s$		
Competitors	Antibody	Mean	(SD)	n^*	Mean	(SD)	n
E. Stand	Ge	−1·555	(0·07)	15^a	−1·114	(0·03)	6^b
Stand 78610	Ge	−1·018	(0·13)	6^c	−0·835	(0·05)	4^d
PAPP-A$_p$	Ge	−1·223	(0·10)	4^e	−1·102	(0·04)	4^f
PAPP-A$_s$	Ge	−1·061	(0·12)	7^g			
E. Stand	Dako	−1·169	(0·08)	5^h	−1·077	(0·02)	4^i
Stand 78610	Dako	−0·879	(0·11)	3^j	−0·742	(0·16)	2^k

^{a} *vs* ^{c}, $P<0{\cdot}005$; ^{b} *vs* ^{d}; $P<0{\cdot}005$; ^{c} *vs* ^{d}, $P<0{\cdot}03$; ^{e} *vs* ^{f}, $P<0{\cdot}05$; ^{e} *vs* ^{g}, $P<0{\cdot}03$, ^{h} *vs* ^{j}, $P<0{\cdot}0005$; ^{i} *vs* ^{k}, $P<0{\cdot}005$; ^{h} *vs* ^{i}, $P<0{\cdot}05$.

* n, Number of different standard curves.

did not modify the slope of the standard curves (Table 1).

The differences in the slope of the standard curves have marked effects on the measurements of PAPP-A in non-pregnant subjects as shown in Table 2. Since the E. Stand and the Stand 78610 are not parallel, one cannot calibrate the one with the other. To overcome this problem we arbitrarily attributed the same concentration of PAPP-A (120 µg/ml) as in the calibrated E. Stand to Stand 78610 (instead of 100 u/l).

Changing from the Geneva anti-PAPP-A to the Dako anti-PAPP-A did not modify the measurable serum concentrations of PAPP-A in the non-pregnant subjects (Table 2). However, the use of Stand 78610 instead of the E. Stand, or ^{125}I-PAPP-A$_s$ instead of ^{125}I-PAPP-A$_p$ decreased significantly ($P<0{\cdot}0005$) the measurable levels of PAPP-A. With ^{125}I-PAPP-A$_s$ and with the E. Stand, the PAPP-A levels were below (in non-pregnant women) or at the concentration (in men) of the first standard point. In contrast, with the same tracer but with Stand 78610, all values were around or below the detection limit of the assay (5 ng/ml).

Adsorbing-out non-pregnant female plasma and serum samples with Dako anti-PAPP-A reduced the measurable levels of PAPP-A below the detection limit of the RIA. Immunoadsorbing the same samples with unrelated anti-sera (to human haptoglobin or human C_3) did not change the measurable levels of PAPP-A (Table 3).

Discussion

As demonstrated by polyacrylamide gradient gel electrophoresis and autoradiography, the PAPP-A preparations contained no detectable contaminant. The single band was recognized by

Table 2. Effects of different variables on the levels of PAPP-A in non-pregnant subjects ($n=7$)

			Non-pregnant female serum (ng/ml)		Male serum (ng/ml)	
Tracer	Type of standard	Antibody	Mean	(SD)	Mean	(SD)
^{125}I-PAPP-A$_p$	E Stand	Ge	53·3	(12·7)^a	49·0	(9 3)^b
^{125}I-PAPP-A$_p$	E. Stand	Dako	45·4	(7·6)^c	43·7	(6·0)^d
^{125}I-PAPP-A$_p$	Stand 78610	Dako	24·3	(5·7)^e	19·1	(6·5)^f
^{125}I-PAPP-A$_s$	E Stand	Dako	14·1*	(5·4)^g	23·4	(3·9)^h
^{125}I-PAPP-A$_s$	Stand 78610	Dako	<5		<5	

* Extrapolated values, detection limit 3–5 ng/ml.

^{a} *vs* ^{c}, NS; ^{b} *vs* ^{d}, NS, ^{c} *vs* ^{e}, $P<0{\cdot}0005$; ^{d} *vs* ^{f}, $P<0{\cdot}0005$; ^{c} *vs* ^{g}, $P<0{\cdot}0005$, ^{d} *vs* ^{h}, $P<0{\cdot}0005$; ^{e} *vs* ^{g}, $P<0{\cdot}0005$; ^{f} *vs* ^{h}, $P<0{\cdot}0005$.

Table 3. Immunoadsorption of plasma and serum samples from non-pregnant females with different antibodies ($n=5$)

		Adsorbed with		
	Not adsorbed	Anti-haptoglobin	Anti-C^3	Dako anti-PAPP-A
EDTA plasma (ng/ml)	44·3 (3·7)	47·8 (3·1)	46·2 (4·1)	<5
Serum (ng/ml)	41·9 (6·1)	39·2 (4·8)	38·2 (3·6)	<5

Results are mean (SD) values.
Measurements were performed with ^{125}I-PAPP-A$_p$, with an EDTA plasma standard and with Ge-anti-PAPP-A.

both anti-PAPP-A antibodies (Ge and Dako) indicating that in the RIA measurable competition by unlabelled proteins will take place only by the 800 kilodalton molecular species. This is in contrast to previously reported results (Bischof *et al.* 1981) where ^{125}I-PAPP-A eluted on a calibrated Sepharose C14B column with an apparent molecular weight of 200 000. This discrepancy could be due to non-specific interactions between ^{125}I-PAPP-A and the Sepharose-C14b matrix.

Depending on the origin of the tracer and the standard (EDTA plasma versus serum), markedly different results are observed: in non-pregnant subjects, PAPP-A levels are either low (if one uses ^{125}I-PAPP-A$_p$ and pregnancy EDTA plasma as a standard) or non-detectable (if one uses ^{125}I-PAPP-A$_s$ and pregnancy serum as a standard).

These differing results are most probably due to an inherent immunological heterogeneity of PAPP-A which might be dependent on blood coagulation since PAPP-A$_s$ and PAPP-A$_p$ do not yield parallel displacement curves irrespective of the antiserum used. The presence of PAPP-A in non-pregnant women is, however, demonstrated by our immunoadsorption study using the Dako antiserum. Clearly the detection of PAPP-A in non-pregnant subjects depends mainly on the nature of the tracer and the standard used in the RIA with few or no effects attributable to the antiserum.

The present observations could explain the different results which appeared in the literature about the presence or absence of PAPP-A in non-pregnant women. In contrast to our RIA, others are using serum-derived tracers and standards. We suggest that this controversy should be accepted as it is until there is more complete understanding of the observed immunological heterogeneity of PAPP-A.

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A fertile woman with non-mosaic Turner's syndrome. Case report and review of the literature

G. H. SWAPP, A. W. JOHNSTON, J. L. WATT, D. A. COUZIN, G. S. STEPHEN

Case report

A 24-year-old white woman was referred at 23 weeks gestation for central maternity hospital booking because of her short stature. Her height was 134·4 cm and she weighed 53·8 kg. The uterus corresponded in size with her dates. In addition to short stature, examination showed webbing of the neck, low hair line, short fourth metacarpals and an increased carrying angle at the elbow. However, she had good breast development. Her menarche was at 14 years and her cycle had been regular (4–5/30). Although women with the characteristic phenotype of Turner's syndrome and a 45,X karyotype generally have primary amenorrhoea, streak gonads and are infertile, a clinical diagnosis of Turner's syndrome was made. Lymphocyte cultures showed a 45,X mitotic karyotype. When aged 7 she had been investigated in a children's hospital for recurring urinary infections and was found to have an absent left kidney. At the same age, after investigation for deafness, she had a left mastoidectomy.

Fetal growth was normal, but an ultrasound scan showed a posterior placenta praevia. It was decided to deliver her by a lower-segment caesarean section 14 days before term. The patient gave permission for skin, fascia and ovarian biopsies to be taken. At caesarean section the ovaries looked normal. A 3400-g boy was born with Apgar scores of 9 and 10 at 1 and 5 min. No congenital malformations were noted. Chromosome analysis on cord blood showed a normal 46,XY karyotype. His subsequent growth and development have been normal. Breast feeding was established and menstruation resumed normally.

Eighteen months later she conceived a second time. Prenatal diagnosis by amniocentesis predicted a 46,XY child and again she was delivered by caesarean section, 14 days before term. Permission was again given for further biopsies to be taken. The child was a normal boy weighing 3620 g, with Apgar scores of 9 and 10. A normal 46,XY karyotype was confirmed on neonatal blood.

Investigations

Cytogenetics. An exhaustive range of her tissues has been examined for evidence of mosaicism (Table 1). Blood was taken on four separate occasions with sampling from multiple sites during the two caesarean sections. G-banding investigations on the initial samples revealed a 45,X karyotype in all cells with a single normal X chromosome. In all, 392 cells from 43 cultures or clones showed a 45,X pattern.

Pathology. The ovaries at caesarean section looked normal in size. A biopsy revealed three ova in 15 levels of tissue examined. Examination of a similar size biopsy from a fertile (46,XX) woman of the same age showed four ova on nine levels.

Xg(a) studies. The proband, her parents and her sons were all Xg(a) positive, so that the family is non-informative as to the parent in which non-

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Table 1. Cytogenetic studies of tissues in a woman with non-mosaic Turner's syndrome

Tissue	Clones or cultures	No. of 45,X cells	Uncultured Barr body −ve cells
Blood	4	255	—
Skin × 2	10	40	18
Fascia	7	35	—
Peritoneum × 2	3	15	50
Skeletal muscle	3	15	—
Uterus	1	2	50
Ovary	15	30	—
Total	43	392	118

disjunction occurred. Nor do they provide evidence against mosaicism.

Discussion

Turner (1938) described a syndrome of infantilism, webbed neck and cubitus valgus. Atria *et al.* (1948) reported the presence of immature oocytes in the ovaries of a 20-year-old woman with the Turner phenotype. Polani *et al.* (1954) suggested that chromatin negative women might be 45,X and later Ford *et al.* (1959) showed this to be the case in women with the Turner phenotype. The earliest report of fertility in such women was by Bahner *et al.* (1960) who described two with Turner phenotype who were menstruating and one had given birth to a healthy boy when aged 31 years. Wray *et al.* (1981) reported a woman of short stature who had given birth to two normal daughters by caesarean section and was then shown to have a 45,X chromosome constitution. They reviewed nine other, apparently non-mosaic, 45,X women and their pregnancies reported in the literature since 1960.

Mosaicism

In only four previous reports (Philip & Sele 1976; King *et al.* 1978; Wray *et al.* 1981; Baudier *et al.* 1985) have multiple tissues been examined (Table 2). Thus, mosaicism involving a 46,XX cell line has not been rigorously excluded in the other patients and, indeed, in the woman reported by Bahner *et al.* (1960) eight cells with 46 chromosomes were recorded out of 92 counted, though none was interpreted as 46,XX. In our patient a total of 392 cells was examined. This excludes mosaicism at the 1% level with greater than 95% confidence (Hook 1977) and is indeed the lowest percentage for exclusion of mosaicism (Table 2). It must be remembered, however, that only two cell types, peripheral lymphocytes and fibroblasts from different tissues, are being investigated.

Table 2. Chromosome studies in 45,X women

			Fibroblasts†					
			Ovary					
Author*	Blood	Marrow	Right	Left	Uterus	Other tissues	Total of 45,X cells	Percentage mosaicism excluded‡
Bahner *et al.* (1960)		51				24	75	4
Philip & Sele (1976)	23,23		48	49	34	26	203	2
King *et al.* (1978)	20+		29	29	29	29,30	166+	2
Nakashima & Robinson (1971)	96					40	136	3
Shokeir (1978)								
Patient 1	+					+,+		
Patient 2	+					+,+		
Kohn *et al.* (1980)	24					48	72	5
Wray *et al* (1981)	32,35		32	24		50,24	195	2
Baudier *et al.* (1985)	20,81		55	+		63	265	2
Present study	255		30		2	105	392	1

*Cases of Grace *et al* (1973), Groll & Cooper (1976) and Lajborek-Czyz (1976) on blood only.
†Fibroblasts (skin, fascia, peritoneum, muscle).
‡Per cent mosaicism excluded with 95% confidence (Hook 1977).

Table 3. Outcome of pregnancies in 45,X women without evidence of mosaicism*

Case reference	Signs	Height (cm)	Breasts	Age at menarche (years)	Menstruation	Presentation	Age at pregnancy (years)	Outcome
Bahner *et al.* (1960)	−	136	+	15	Regular		31	Normal male (chromatin −ve)
Nakashima & Robinson (1971)	+	124	+	16	Irregular	Short stature, delayed development	21	Normal 46,XX
Grace *et al.* (1973)	−	137	+	13	Irregular	Amenorrhoea	22	Normal 46,XX
Lajborek-Czyz (1976)	±	Short	+	14	Irregular	? via Down's baby	22	Down's syndrome 47,XY +21
Groll & Cooper (1976)	±	154	+	13	Regular	Amenorrhoea	25	Stillbirth, cord complications (normal female)
							27	Normal female
Philip & Sele (1976)	−	142	−	Oestrogens		Delayed development, short stature	30	Hydrocephalus at 26 weeks
							?33	Normal 46,XY
King *et al.* (1978)	±	138	+	Oestrogens	Later regular	Short stature, delayed development	21	Normal 46,XY
Shokeir (1978)								
Patient 1	+	137·5	+	14	Irregular	Secondary amenorrhoea	16	Abortion 14 weeks
Patient 2	+	140	+	13	Regular	Secondary amenorrhoea	15	Normal male
Kohn *et al.* (1980)	+	140	+	14	Regular	Amenorrhoea	24	Two miscarriages at 3 months
							24	
Wray *et al.* (1981)	+	127	+	15	Regular	Hypothyroidism and short stature	23	Normal 46,XY
							26	46,XX (+ cleft palate)
Baudier *et al.* (1985)	+	Short	(+oestrogens)	Oestrogens	Irregular (oestrogen therapy)	Delayed development	21	Miscarriage
							23	Twin miscarriage
							25	Normal 46,XY
							26	Normal 46,XY
Present study	+	135	+	14	Regular	Short stature in pregnancy	24	Normal 46,XY
							26	Normal 46,XY

± indicates two minor signs of Turner phenotype.

* There were 14 normal outcomes of 21 pregnancies in 13 women.

Table 4. Outcome of pregnancies in women with 45,X mosaicism

					Stillbirths			Livebirths			
Reference†	No of women	No of pregnancies	Normal	Miscarriage	Normal	Preterm	Abnormal*	Abnormal*	Down's syndrome	45,X mosaic	Neonatal death
1	24	57	18	15	1		3	12	3	5	
2	5	12	2 (1 twin)	7	2 (1 twin)			1			Twins
3	6	10	8	2							
4	2	18	6	8		3				1	
Total	37	97	34	32	3	3	3	13	3	6	2

* Various congenital abnormalities

† Reference 1=Nielsen *et al* (1979), 2=Mavel *et al* (1980); 3=Combined data reported by Dinkelmann & Landolt (1981), Badawy *et al* (1981), de Grouchy *et al* (1981), Formiguera Sala *et al* (1982), Kable & Yussman (1981) and McCorquodale & Bowdle (1985), 4=Ayuso *et al* (1984)

Outcome

Table 3 details the outcome of 21 pregnancies in 13 non-mosaic women; there were 14 normal children, one of whom was stillborn and one had familial cleft palate. There was one Down's syndrome (47,+21) and one congenital abnormality (hydrocephalus). The remaining five pregnancies, which included one twin pregnancy, ended in miscarriage.

Table 4 summarizes the reports of 37 women with Turner mosaicism who had conceived at least once; overall there were 97 pregnancies, of which 34 resulted in the birth of a normal live child who survived. Cytogenetic studies were rarely performed. However, chromosome abnormalities were identified in nine, of which three were Down's syndrome (47,+21) and no fewer than six showed mosaicism with a 45,X cell line. This strongly suggests that in these women there is repeated non-disjunction with one X chromosome behaving abnormally in meiosis and mitosis. Of the 97 pregnancies 32 ended in miscarriage and nine in stillbirth, of which only three were reported to be normal. Ayuso *et al.* (1984) reported that one patient had had three miscarriages at 5 or 6 months gestation. Three stillbirths were specifically noted to have congenital abnormalities, as did 13 of the liveborn children and, in addition, there were the nine with a chromosome abnormality. One pair of twins was born preterm, both dying in the first 4 days, and one of another pair of dizygotic twins was stillborn.

Thus, only one-third of these pregnancies resulted in a normal surviving child. Even if the six 45,X mosaic girls were included as normal, the success rate for pregnancy is considerably less than for the women with non-mosaic Turner's syndrome. The offspring of mosaic women comprise an excess with Down's syndrome and also an excess of congenital malformations.

Whether these differences in outcome between the mosaic and non-mosaic women are significant is uncertain with these numbers.

The aetiology is also uncertain; ascertainment of girls with 'fertile' Turner's syndrome is especially likely to fail where there is ovarian function and consequent breast development.

Previous authors (Reyes *et al.* 1976; Otto *et al.* 1977) have commented on the difficulty in obtaining reliable risk figures for chromosome abnormalities in the offspring, but this review suggests that the risk for non-mosaic mothers is not as great as had been thought. However, it is clear that the reproductive span is shorter than normal. Prenatal diagnosis was performed in our patient's second pregnancy, but will not always be acceptable.

Mechanism of oogenesis

It has long been known that female mice with only one X chromosome (39,X) are fertile, but have a shortened reproductive span. Such mice are born with only about half the number of oocytes that their 40,XX littermates have. This deficiency is due to excessive atresia of oocytes at pachytene in the perinatal period. Speed (1986) studied oocyte development in three 45,X human fetuses at 15, 17 and 24 weeks gestation. He concluded that in contrast to mice, human fetuses showed severe germ cell arrest at early prophase (preleptotene stage). The single X element remains free, while in the mouse at pachytene it pairs non-homologously on itself forming a loop or hairpin or a triradial with a pair of autosomes. Speed (1986) suggested that these mechanisms could occur in man, allowing the oocytes to survive into the adult ovary. One could speculate that heterologous pairing involving chromosome 21 could account for the excess of Down's syndrome. However, it could be a non-specific effect on chromosomal segregation or reflect a prematurely ageing ovary.

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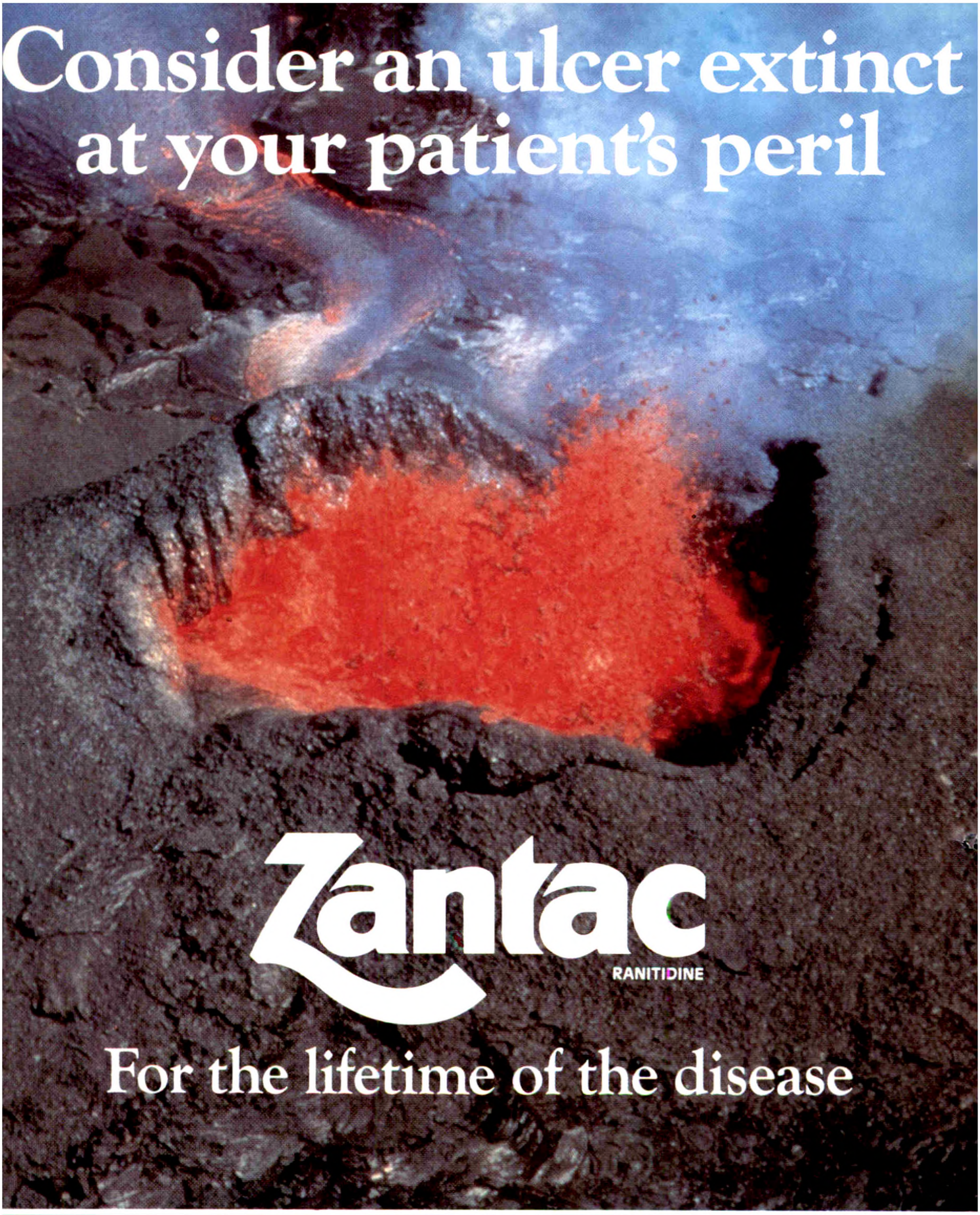

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CORRESPONDENCE

Suppression of gonadotrophin secretion does not reverse premature ovarian failure

Dear Sir,
The recent paper by Ledger *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 196–199] describes the results of prolonged inhibition of gonadotrophin secretion in patients with premature ovarian failure. The conclusion of the authors is that suppression of gonadotrophin secretion does not reverse premature ovarian failure.

We have had a similar experience with four women with premature ovarian failure. All had had secondary amenorrhoea of at least 1 year's duration and a plasma FSH of >20 iu/l on at least two occasions. They were given a single dose of goserelin, 3·6 mg subcutaneously, and adequate suppression of LH and FSH was found in all patients. After 4 weeks buserelin was given intranasally, 400 μg thrice daily, in combination with human menopausal gonadotrophins (hMG) for the induction of ovulation. Plasma concentrations of oestradiol did not rise during treatment, and pelvic ultrasonography failed to demonstrate follicular growth.

These observations indicate that the combination of inhibition of gonadotrophin secretion, followed by administration of hMG for ovulation induction, also does not reverse premature ovarian failure.

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Reference

Ledger W. L , Thomas E J , Browning D , Lenton E. A. & Cooke I D. (1989) Suppression of gonadotrophin secretion does not reverse premature ovarian failure. *Br J Obstet Gynaecol* **96**, 196-199.

Vaginal ultrasound for ruling out placenta praevia. Case report

Dear Sir,
We are somewhat concerned with the management of placenta praevia as described by Farine *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 117–119]. Having diagnosed a type III placenta praevia by abdominal ultrasound they deem it safe to pass a vaginal probe, yet in the discussion they state that a digital examination 'exposes the patient to the risk of major haemorrhage'. Would this not be true also for a vaginal ultrasound probe?

We agree with their comments on the limitations of abdominal ultrasound in later pregnancy, but in our experience can achieve a similar accuracy by abdominal scanning as they claim by vaginal scanning (they give a 2 cm range for the distance of the placenta from the internal os). Generally we find that encouraging the patient to have a full bladder (if necessary with the aid of a catheter) will improve the accuracy of an abdominal scan.

Finally we strongly disagree with their conclusion that a single case report of the use of a vaginal ultrasound probe demonstrates this to be a safe procedure in placenta praevia, especially as the case described was only type I placenta praevia. Performing the same procedure in type III or IV placenta praevia could well have resulted in massive haemorrhage.

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Reference

Farine D., Fox H. E. & Timor-Tritsch I (1989) Vaginal ultrasound for ruling out placenta praevia Case report *Br J Obstet Gynaecol* **96**, 117-119.

Authors' reply

Dear Sir,

We appreciate the concerns expressed by Drs Neale and Rogers with regard to the transvaginal scanning of patients with suspected placenta praevia.

However, we would like to reassure them that there seems to be no place for concern in performing this ultrasound examination. The reason for it is explained in the article itself, i.e. the tip of the probe will usually be as far as 3 cm from the cervix itself, in order to be able to reproduce the region of interest (the internal os) on the screen. If one is familiar with the physics of this probe and its specifications, it becomes immediately clear that there is absolutely no danger in introducing the probe under direct vision, through its entire route until it is in place, and once again we emphasize it will not touch the cervix at all

We agree with the statement that it is very difficult to conclude from one single case report that this is a safe procedure, but we would like to draw their attention to our publication (Farine *et al.* 1988) which describes our experience with 35 patients with suspected placenta praevia, scanned vaginally. Regardless of the presence or absence of a placenta praevia in these patients, there was no bleeding encountered. At the present time, we scanned a little over 70 patients of whom 25 had placenta praevia (marginal or central), and none of these had any vaginal bleeding. The same experience is now shared by many medical centres which perform this ultrasound scanning for all patients with suspected placenta praevia.

The moment the initial fear of the sonographer is overcome by experience and by observing the relation between the internal os and the placenta, one can hardly go back and use the classical transabdominal method.

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Reference

Farine D., Fox H. E., Jacobson S. & Timor-Tritsch I E (1988) Vaginal ultrasound for diagnosis of placenta previa. *Am J Obstet Gynecol* **159**, 566-569.

Transmission of human immunodeficiency virus by heterosexual contact with reference to antenatal screening

Dear Sir,

We would like to support the conclusions of Howard *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 135–139] from the slightly different perspective of Edinburgh. From 1985 in East Riverside, an area of London with a high frequency of HIV infection, these authors identified 40 women who were seropositive There were 15 pregnancies. The authors point to the importance of heterosexual transmission, plan to continue offering HIV testing to all antenatal women, and recommend total anonymous screening in pregnancy to establish HIV prevalence.

By comparison, in Edinburgh, there are 267 women known to be infected (CDS 1989), 150 of whom are attending the City Hospital Clinic (Brettle *et al.* 1987). Most have been infected through injected drug use, but heterosexual transmission appears to have been the mode of infection in 20% of cases. There have been 107 pregnancies where the woman has been known to be seropositive. This known prevalence is approximately 0·4% of all pregnancies in Edinburgh City residents, and as only 1·6% of the pregnant population were tested, this will be an underestimate. HIV infection in women is thus a major problem, and the risk of heterosexual spread is serious.

Like Howard *et al.* we believe that surveillance and testing for patient information are separate issues. Surveillance is important, and is best done by total anonymous screening. Little can be made of data where the expected prevalence is small and 26% of the population refuse testing, as in the Riverside study. However, where there is an appreciable prevalence, we also believe that all pregnant women should be offered attributable testing (with counselling and informed consent). There are now significant advantages for a pregnant woman and her child in knowing that she is infected, as recently discussed by Minkoff & Landesmann (1988).

In an editorial in the same issue of your Journal, Johnson & Webster (1989) take the opposing view about anonymous testing. They 'doubt the clinical wisdom of being unable to identify and counsel a pregnant woman when the prognosis for her and her infant is so poor'. This seems typical of the muddled thinking that has characterized this debate. Anonymous screening is not an alternative, but is complementary to attributable testing. It provides data where none would otherwise be available. Although clinical management of individual patients is our priority, basic epidemiological information is important in planning health care and future strategy to combat this disease, and these two elements of screening should not be confused in this way.

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BOOK REVIEWS

Clinical Practice in Sexually Transmissible Diseases. Second edition by D. H. H. Robertson, A. McMillan & H. Young. Churchill Livingstone, Edinburgh, 1988, 520 pages with figures and tables, £49.50

'Scholarly' is the word that comes to mind as a single adjective to describe this book. It is long and comprehensive, and contains much that is of interest rather than strictly of practical use. Gynaecologists, like genitourinary physicians, need to read round their subject, and much valuable common ground is covered here in chapters on sexuality, health education, ethics, sociology and medico-legal matters.

There then follow almost 100 pages on syphilis and the treponematoses. Even for genitourinary physicians this is probably not all needed but the story of this classic infection makes fascinating reading. Gonorrhoea then receives coverage followed by all the other sexually transmitted conditions and some infections of the genital tract which are not due to sexually transmitted agents. In all the authors have produced a classic reference text for their speciality.

Therein lies the weakness; the book is probably too classic and rigidly traditional in its approach. Colposcopy, regarded by many genitourinary physicians as an essential tool for the future, merits a short footnote only. Laparoscopy is no better covered; it is branded as dangerous with a 6% risk of complications including bowel perforation, mesenteric haemorrhage and haematoma and abscess formation. The authors are clearly not aware of the DHSS/RCOG report of 12 years ago! The index is also weak; for example bartholinitis is not listed, and anyone wishing to research this common condition from this book would have great difficulty (and find little in the end).

This book is a classical volume in the old tradition of venereology. Whilst keeping up to date in strictly medical fields such as AIDS it is weak in the field of genital infection in women. It makes fascinating reading, but cannot be recommended as a practical reference volume for gynaecology units.

M. J. Hare

The Menopause edited by John W. W. Studd & Malcolm Whitehead. Blackwell Scientific Publications, Oxford, 1988, 312 pages with figures and tables, £49.50

Between the fixed points of birth and death, most events in human life are to some extent optional. Even basic processes such as formal education, pregnancy and the paying of taxes can be set aside in certain circumstances, but in a list of inevitable events in the life of a woman, the experience of the menopause is unavoidable unless medical intervention is sought.

Although the menopause and its consequences have affected women throughout the centuries if they live long enough, a great expansion in the medical understanding of the subject came in the 1960s and 1980s with the introduction of sensitive assays to let us measure the steroid and peptide hormone changes which are a major feature of the menopause transition. To a great extent it is in the 1980s that the large body of research on the menopause in all its aspects has come to fruition, and gradually in the last decade women and pressure groups have become much more vocal in their requests for help to deal with the problems which can occur. Several British groups have contributed to our understanding of the menopause and its treatment, but there can be little doubt that the editors of this volume, John Studd and Malcolm Whitehead, have made a particularly prominent contribution. They are well placed to put together an assessment of the state of the art in this field for the late 1980s. Being practical clinicians as well as researchers, they have produced a volume which deals with both the physiology and pathophysiology of the menopause, and also provides chapters dealing with practical considerations for the clinician providing treatment.

These practical considerations are seldom given the weight and consideration they deserve in textbooks. In this volume this is corrected. The 25 chapters include 14 from authors in this country and 11 from overseas. There is an understandable bias towards British authors who are associated with the King's menopause clinics, who provide 10 chapters. The overseas authors could not be better chosen and include many of the world's leading figures. In this list can be included what might be the final appearance in print of the late Professor Robert Greenblatt. His foreword to the book reminds us of the breadth and humanity of this major pioneer and father figure.

One topic which I would like to have seen given a clear exposition is the pharmacology of the different progestogens since the choice and dose of progestogens is an important determinant of the regimen employed. Although many points relating to these can be gleaned from the different chapters, I would have welcomed a coherent account of this topic as an individual chapter. I was interested to note that this very approach was adopted in a recent American textbook on the menopause with an excellent chapter on progestogens provided by Malcolm Whitehead himself.

This is a timely publication and can be read with value by both specialists and generalists. Since the treatment of the menopause is also very much a general practice matter it would be a book well worth having in every practice, and since there is now so much drug company interest in this field I would also recommend it as standard issue for pharmaceutical representatives involved with hormone replacement therapy.

David H. Barlow

Twinning and Twins edited by I. MacGillivray, D. M. Campbell & B. Thompson. John Wiley & Sons, Chichester, 1988, 321 pages with figures and tables, £52.50

There is a surprising paucity of books about twins and twin pregnancy but there is a plethora of publications about the subject. This book is therefore a particularly welcome addition to the medical literature. With contributions from distinguished clinicians and epidemiologists in a series of 14 chapters on all aspects of twin pregnancy, the book also contains an extensive bibliography of some 900 references.

It does not always make easy reading with the concentrated exposition of tables and figures extracted from the world literature, but I can think of no other publication that approaches the quality of this volume as a review of twin pregnancy.

Ian MacGillivray has dedicated a substantial part of his research career in Aberdeen to promoting interest in the nature and problems of twin pregnancy and, in one sense, this book is a tribute to that work. There are chapters on zygosity determination, descriptive epidemiology, physiological adaptation, antenatal and intrapartum management and later growth and intelligence. Inevitably, there are some aspects that are probably changing and on which there are few facts at present. For example, the use of genetic finger-printing may enhance the accuracy of determining zygosity in the future. Incidence figures are being modified by the use of ovarian stimulants. One suspects that factors that bear no relation to reasonable obstetric practice may conspire to alter the pattern of delivery and we shall see an increasing tendency towards elective caesarean section for twins as well as an increasing section rate for second twins. These are matters for the future.

For the present, this is an excellent contribution to the literature and an invaluable reference source for research workers planning studies or teaching about twin pregnancy.

This is a book that should be on the shelf of all practising obstetricians and neonatal paediatricians. It has my strongest recommendation.

E. M. Symonds

Gynecologic Surgery edited by Luis E. Sanz. Medical Economic Books, New Jersey, 1988, 400 pages with figures and tables, $57.95

This multi-author volume is written in several subsections, which include the principles of general surgery and anatomy, vaginal surgery, gynaecological urology, infertility surgery, laser surgery and postoperative complications. The text does not cover all aspects of gynaecological surgery because there is no section on the management of malignant disease or the surgery of vulval disease. Surprisingly, simple abdominal hysterectomy is not included. In the section on infertility surgery there is no discussion on the laparoscopic assessment of the infertile woman and the assessment of tubal disease via the laparoscope.

Each section and subsection is written by an expert practical surgeon, and the chatty nature of the text reflects the personal experience of each individual writer. I find this method of writing quite instructive. The book is well illustrated with multiple diagrams and although it is always difficult to show operative techniques in diagrammatic form, this book manages clarity with simple clear line drawings. There are a few photographs, which are less than satisfactory, showing endoscopic laser ablation of endometriotic implants but there is a series of colour pictures in the centre of the book that are of high quality.

I think this is a publication which is well suited to the postgraduate registrar in training for the MRCOG examination and I would recommend it.

B. Victor Lewis

Books received some of which will be reviewed at a later date

Statistics with Confidence. Confidence Intervals and Statistical Guidelines by Martin J. Gardner & Douglas G. Altman. *British Medical Journal*, London, 1989, 140 pages with tables, UK £7.95, abroad £9.50, USA $19.00 including postage by air. The book can be ordered by post from the *British Medical Journal*, PO Box 295, London WC1H 9TE

Advances in Clinical Andrology edited by C. L. R. Barratt & I. D. Cooke. MTP Press Ltd, Lancaster, Boston, The Hague, Dordrecht, 1988, 118 pages with figures and tables, Dfl 94.00, US $47.00, UK £25.00

Dennen's Forceps Deliveries Third edition by Philip C. Dennen. F. A. Davies Co., Philadelphia, 1989, 201 pages, fully illustrated, £23.34

Neurology of Pregnancy Second edition by James O. Donaldson. W. B. Saunders Co., London, Philadelphia, 1989, 347 pages with figures and tables, £35.00

Antepartum and Intrapartum Management by Julian T. Parer. Lea & Febiger, Philadelphia, London, 1989, 264 pages with figures and tables, £18.44

Prolactin and Lesions in Breast, Uterus and Prostate edited by Hiroshi Nagasawa. CRC Press, Inc., Boca Raton, Florida, 1989, 229 pages with figures and tables, $145.00

Heart Disease in Women (Cardiovascular Clinics Volume 19 Number 3) edited by Pamela S. Douglas. F. A. Davis Co., Philadelphia, 1989, 335 pages with figures and tables, $75.00

Year Book of Perinatal/Neonatal Medicine 1988 edited by Marshall H. Klaus & Avroy A. Fanaroff. Year Book Medical Publishers. Inc., Chicago, London, Boca Raton, 1989, 344 pages, £35.50

Errata

Br J Obstet Gynaecol **96**, 697–704

Evidence of redistribution of cardiac output in asymmetrical growth retardation
W. AL-GHAZALI, S. K. CHITA, M. G. CHAPMAN & L. D. ALLAN

Table 3. In fetus no. 9 the combined cardiac output (CCO) was 209 ml/min and not 650 ml/min as stated in the Table.

On page 699, left-hand column, line 25 of the paragraph headed *Symmetrical growth retardation* should read 'The other 11 were thought to be genuinely growth retarded . . .'

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COMMENTARIES

Rubella infection in pregnancy: remaining problems

Last year all doctors in the UK were sent a small green handbook entitled *'Immunization against Infectious Disease'*. Inside its covers there is explanation and advice on the use of some 20 vaccines including the new measles/mumps/rubella (MMR) vaccine. This was launched in place of single antigen measles vaccine in October 1988 as part of a major new immunization initiative which has as its aim the elimination of measles, mumps and rubella in the UK. The new vaccination programme should be of special interest to obstetricians since, as explained in the handbook, the main impetus for its introduction is to prevent the continuing problem of rubella infection in pregnancy and its tragic consequences.

Rubella vaccine was first introduced in the UK in 1970 for the vaccination of schoolgirls and non-immune women and has substantially reduced the incidence of congenital rubella syndrome (CRS). However, about 20 cases of CRS still occur each year and a further 100–200 women, in whom rubella is diagnosed during pregnancy, have a legal abortion. The reason for the continuing occurrence of such cases is that a small proportion (2–3%) (Miller *et al.* 1985, 1987) of pregnant women are susceptible to rubella, either because they have not been offered or have refused vaccine, or have failed to seroconvert after vaccination. The objective of vaccinating children is to prevent circulation of the virus and so protect susceptible pregnant women from exposure. The success of this policy will depend on achieving a vaccine uptake of at least 90% in young children and there are already encouraging signs that this will be possible despite the previously low uptake for measles vaccine. However, until this is achieved and rubella is eliminated in the UK, the selective vaccination of schoolgirls and adult women must continue. Similarly, the need for full serological investigation of pregnant women who present with a rash, or who report contact with rubella, will remain.

Achieving a correct diagnosis of primary rubella infection is of critical importance when the woman is in the first 4 months of pregnancy, as the consequences for the fetus are likely to be devastating (Miller *et al.* 1982). The risk to the fetus appears to be similar whether the primary infection is accompanied by a rash or remains subclinical (Cradock-Watson *et al.* 1981). For this reason it is necessary to investigate asymptomatic pregnant contacts as well as women who present with a rash Even when clinically typical symptoms are present, serological confirmation of the diagnosis should still be sought since fewer than half such cases are likely to be attributable to rubella (Cradock-Watson *et al.* 1973). Some women with a rubella-like illness will have been screened for rubella antibody in the past and reported immune. Full serological investigation is nevertheless required because of the possibility of earlier error. Among nearly 1000 pregnant women with confirmed symptomatic rubella reported to the Communicable Disease Surveillance Centre over the period 1983–1987, 23 (2%) had been screened in the past and were reported to have antibody present; nine congenitally infected infants were identified among the 15 pregnancies that continued to term. In some cases the earlier test was with the older haemagglutination inhibition method that, unlike the radial haemolysis method, can give rise to so-called 'false-positives'. In other cases radial haemolysis was used but a technical or clerical error was discovered retrospectively. It is for reasons such as this that the Royal College of Obstetricians and Gynaecologists recommends that women should be screened for rubella antibody in every pregnancy irrespective of an earlier positive result.

Pregnant women with a record of vaccination and who present with a rash or who have been in contact should also be investigated because of the possibility of vaccine failure. This occurs after 2–5% of vaccinations; no antibody is produced and on subsequent exposure to rubella virus there is a typical primary antibody response with IgG seroconversion and a high concentration of specific IgM which persists for at least a month. Primary vaccine failure should be distinguished from a vaccine response which, over time, declines to below the 15 iu/ml antibody level regarded as protective. This can occur after natural rubella as well as vaccination and in such cases reinfection with wild rubella virus, or revaccination, produces a booster rather than a primary response. This is characterized by a rise in IgG antibody with a negative or low level IgM response. Such responses may also occur in women with antibody levels above 15 iu/ml at the time of contact, indicating that reinfection is not simply a consequence of exposure in a woman with waning antibody levels.

Reinfections are usually asymptomatic and are most commonly detected in women who have close and prolonged exposure, for example when their own children have rubella. Unlike primary rubella in early pregnancy which presents a substantial risk to the fetus, the risk of reinfection has been considered minimal. There have been a number of published reports attributing congenital rubella to maternal reinfection in pregnancy, but in many the evidence of prior antibody in the mother has not been convincing (Morgan-Capner 1986). However, five cases of fetal infection resulting from confirmed maternal reinfection have recently been reported in the UK (J. M. Best, personal communication) suggesting that the risk may be higher than previously supposed. The only two prospective studies of the outcome of reinfection in pregnancy found no cases of congenital infection among 41 pregnancies that continued to term (Cradock-Watson *et al.* 1981; Morgan-Capner *et al.* 1985). Although this is reassuring, the numbers followed up are small, particularly among women whose initial antibody was vaccine induced.

Clearly there is a need to obtain more precise information on the risk of maternal reinfection, and a prospective study of the outcome of such cases is being organized by the Public Health Laboratory Service (PHLS). Obstetricians caring for patients in whom reinfection has been diagnosed are asked to send cord blood samples to the Communicable Disease Surveillance Centre for specific IgM antibody testing. Detection of IgM antibody in fetal blood can also be used for prenatal diagnosis but unfortunately the practical value of this technique in managing women with reinfection is limited since IgM may not appear in fetal blood until after 23 weeks despite intrauterine infection early in pregnancy (Enders & Jonatha 1987). Isolation of rubella virus from amniotic fluid has also been used for prenatal diagnosis (Hayes *et al.* 1982) but culture is a relatively insensitive method of detecting the virus and, if successful, may take up to 6 weeks to obtain the result. Reliable techniques of prenatal diagnosis which are applicable in early pregnancy are therefore required. The technique of chorionic villus sampling together with nucleic acid hybridization has been successfully used to diagnose congenital rubella infection as early as 15 weeks gestation (Terry *et al.* 1986) and could in theory be used as early as 8–10 weeks. However, further studies to validate this technique are required.

In view of the current uncertainty about the risk to the fetus of maternal reinfection, what should be the advice to asymptomatic pregnant women who present with a history of home contact with rubella and who have had two or more positive tests by radial haemolysis in the past? Under these circumstances the likelihood of repeated technical or clerical error is remote and the main purpose of diagnostic investigation then becomes to identify a possible reinfection. However, deciding on a course of action should asymptomatic reinfection in early pregnancy be diagnosed can pose considerable problems since the risk, although low, is not precisely known. On the available evidence it is reasonable to presume that the risk of fetal infection is less than 10%, and probably less than 5%. However, it is not zero and in the event of a rubella-damaged baby being born there could be serious medico-legal consequences if the parents were not informed of the risk at the time of diagnosis. Careful counselling of the parents is therefore necessary but inevitably considerable anxiety will be generated and many unnecessary abortions will be performed. The decision to investigate rather than reassure pregnant contacts who have had repeated positive tests by radial haemolysis must therefore rest on individual clinical judgement. It is to be hoped that the introduction of MMR vaccine for young children will provide the long-term solution to the problem of reinfection by preventing rubella contact during pregnancy in the future.

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Revised FIGO staging for gynaecological cancer

The FIGO Gynaecological Oncology Committee met in Rio de Janeiro in October 1988 and revised the staging of gynaecological cancers.

Carcinoma of the uterine corpus

The Committee decided that corpus cancer should be surgically staged and as a result additional factors of prognostic importance are included in the staging. The Committee also decided to change the current definitions of tumour grading to coincide with the new recommendations of the International Society of Gynaecological Pathologists. The recommended staging is as follows:

Stage

IA	G123	Tumour limited to endometrium
IB	G123	Invasion to <1/2 myometrium
IC	G123	Invasion to >1/2 myometrium
IIA	G123	Endocervical glandular involvement only
IIB	G123	Cervical stromal invasion
IIIA	G123	Tumour invades serosa and/or adnexa and/or positive peritoneal cytology
IIIB	G123	Metastases to pelvic and/or para-aortic lymph nodes
IVA	G123	Tumour invasion of bladder and/or bowel mucosa
IVB		Distant metastases including intra-abdominal and/or inguinal lymph nodes

Histopathology: degree of differentiation

Cases of carcinoma of the corpus should be grouped with regard to the degree of differentiation of the adenocarcinoma as follows:

G1	5% or less of a non-squamous or non-morular solid growth pattern.
G2	6–50% of a non-squamous or non-morular solid growth pattern.
G3	More than 50% of a non-squamous or non-morular solid growth pattern.

Notes on pathological grading

(1) Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade I or grade II tumour by one.
(2) In serous adenocarcinomas, clear-cell adenocarcinomas, and squamous-cell carcinomas, nuclear grading takes precedence.
(3) Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rules related to staging

(1) Since corpus cancer is now surgically staged, procedures used previously for the differentiation of stages are no longer applicable, such as using dilatation and curettage findings to differentiate between stage I and stage II. (It is appreciated that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 would still apply but designation of that staging system would be noted.)
(2) Ideally, the thickness of the myometrium should be measured along with the depth of tumour invasion.

Vulval cancer

The Committee recommended that the following changes in vulva staging should be implemented: that the involvement of the perineum will no longer mean an automatic stage III categorization; also the inguinal lymph node involvement criteria have been changed so that current staging is as follows:

Stage 0

Tis	Carcinoma *in situ*, intraepithelial carcinoma

Stage I

T1 N0 M0	Tumour confined to the vulva and/or perineum, ≤ 2 cm in greatest dimension, nodes are not palpable

Stage II

T2 N0 M0	Tumour confined to the vulva and/or perineum, ≥ 2 cm in greatest dimension, nodes are not palpable

Stage III

T3 N0 M0	Tumour of any size with
T3 N1 M0	(1) Adjacent spread to the lower urethra and/or the vagina, or the anus, and/or
T1 N1 M0 T2 N1 M0	(2) Unilateral regional lymph node metastasis

Stage IVA

T1 N2 M0	Tumour invades any of the following:
T2 N2 M0	Upper urethra, bladder mucosa, rectal mucosa, pelvic bone and/or bilateral regional node metastasis
T3 N2 M0 T4 any N M0	

Stage IVB

Any T, any N M1	Any distant metastasis including pelvic lymph nodes

Rules for clinical staging

The rules for staging are similar to those for carcinoma of the cervix.

TNM classification of carcinoma of the vulva (FIGO)

T	*Primary tumour*
Tis	Pre-invasive carcinoma (carcinoma *in situ*)
T1	Tumour confined to the vulva and/or perineum, ≤ 2 cm in greatest dimension
T2	Tumour confined to the vulva and/or perineum, >2 cm in greatest dimension
T3	Tumour of any size with adjacent spread to the urethra and/or vagina and/or to the anus
T4	Tumour of any size infiltrating the bladder mucosa and/or the rectal mucosa including the upper part of the urethral mucosa and/or fixed to the bone

N	*Regional lymph nodes*
N0	No nodes palpable
N1	Unilateral regional lymph node metastasis
N2	Bilateral regional lymph node metastasis

M	*Distant metastasis*
M0	No clinical metastasis
M1	Distant metastasis (including pelvic lymph node metastasis)

Ovarian cancer

A minor change was made in the ovarian cancer staging as there has been some confusion raised about stage Ia and Ib with regard to ascites. The Committee has recommended that stage Ia and b should include the following: 'No ascites present containing malignant cells'. Thus, significant free fluid with malignant cells would be included in stage Ic as defined previously in 1985, as follows:

Stage

I	Growth limited to the ovaries
Ia	Growth limited to one ovary; no ascites; no tumour on the external surface; capsule intact
Ib	Growth limited to both ovaries; no ascites; no tumour on the external surfaces; capsule intact
Ic*	Tumour either Stage Ia or Ib, but with tumour on surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
II	Growth involving one or both ovaries with pelvic extension
IIa	Extension and/or metastases to the uterus and/or tubes
IIb	Extension to other pelvic tissues
IIc*	Tumour either Stage IIa or IIb but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings
III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver metastases equals Stage III; tumour is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum
IIIa	Tumour grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIb	Tumour involving one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces none exceeding 2 cm in diameter; nodes are negative
IIIc	Abdominal implants greater than 2 cm in diameter and/or positive retroperitoneal or inguinal nodes
IV	Growth involving one or both ovaries with distant metastases. If pleural effusion present, there must be positive cytology to allot a case to Stage IV; parenchymal liver metastasis equals Stage IV.

*To assess the impact prognosis of the different criteria for allotting cases to Stage Ic or IIc it would be of value to know whether the source of malignant cells was (i) peritoneal washings or (ii) ascites, and whether rupture of the capsule was spontaneous or caused by the surgeon.

Cervix cancer

The definition of the clinical stages in carcinoma of the cervix uteri remain the same as agreed and defined in 1985. It should be remembered that at that time the definition of micro-invasion was altered and the term 'occult' abandoned. Current staging is as follows:

Stage

0	Carcinoma *in situ,* intraepithelial carcinoma; *cases of Stage 0 should not be included in any therapeutic statistics for invasive carcinoma*
I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded)
Ia	Preclinical carcinoma of the cervix, that is those diagnosed only by microscopy
Ia1	Minimal microscopically evident stromal invasion
Ia2	Lesions detected microscopically that can be measured; the upper limit of the measurement should not show a depth of invasion of >5 mm taken from the base of the epithelium, either surface or glandular, from which it originates; a second dimension, the horizontal spread, must not exceed 7 mm; larger lesions should be staged as Ib

Ib Lesions of greater dimension than Stage Ia2 whether seen clinically or not; preformed space involvement should not alter the staging but should be specifically recorded so as to determine whether it should affect treatment decisions in the future

II The carcinoma extends beyond the cervix, but has not extended on to the pelvic wall; the carcinoma involves the vagina, but not as far as the lower third

IIa No obvious parametrial involvement

IIb Obvious parametrial involvement

III The carcinoma has extended on to the pelvic wall; on rectal examination there is no cancer-free space between the tumour and the pelvic wall; the tumour involves the lower third of the vagina; all cases with a hydronephrosis or non-functioning kidney should be included, unless they are known to be due to other cause

IIIa No extension on to the pelvic wall, but involvement of the lower third of the vagina

IIIb Extension on to the pelvic wall *or* hydronephrosis or non-functioning kidney

IV The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum

IVa Spread of the growth to adjacent organs

IVb Spread to distant organs

These definitions should be implemented for contributions to the next annual report to be compiled in 1991 for reporting in 1992 in Singapore.

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Oocyte donation: a review

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Summary. Oocyte donation provides an option for achieving pregnancy in women lacking functioning gonads, or in whom IVF techniques have failed to harvest adequate oocytes, or those who do not wish to use their own gametes because of hereditary disease. In agonadal women, artificial menstrual cycles are required before proceeding to gamete donation. A fixed cyclical steroid replacement schedule of oestradiol (E_2) valerate and progesterone (P_4) pessaries was initially used, but the need for synchrony between donor and recipient cycles, and the narrow window for implantation limited the transfer of fresh embryos. Donor–recipient cycle asynchrony can be overcome by using frozen-thawed embryos, or by extending the follicular phase in the recipient to widen the transfer window. Twenty-two pregnancies have now been achieved by the Monash/Epworth group, resulting in the birth of 13 healthy infants. There were no statistically significant differences in pregnancy rates (per transfer) between transfers in natural cycles (14%, four pregnancies) and steroid replacement cycles (24%, 16 pregnancies). Five pregnancies (36%) were established in women treated with 2 mg of E_2 daily 13–18 days before embryo transfer with P_4 starting on the day of or the day following oocyte retrieval. E_2 was continued for a median of 85 days (range 49–110) and P_4 for a median of 86 days (range 49–133) after the supposed last menstrual period. All but one delivery was by caesarean section. There were no perinatal deaths and no ectopic pregnancies.

The concept of gamete donation is not new. Donor insemination has been a recognized and acceptable method of infertility treatment for many years, but it has only been with the development of in-vitro fertilization (IVF) techniques that it has been possible to consider oocyte donation.

The first pregnancy derived from a donated oocyte resulted in miscarriage (Trounson *et al.* 1983); however, some months later Lutjen *et al.* (1984) reported a successful pregnancy in a woman with ovarian failure who had received an embryo derived from an anonymously donated oocyte. Others have reported similar successes (Asche *et al.* 1987; Chan *et al.* 1987; Feichtinger & Kemeter 1985; Navot *et al.* 1986; Rosenwaks *et al.* 1986; Salat-Baroux *et al* 1988), and oocyte

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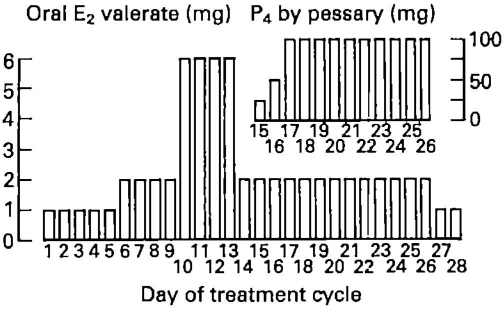

Fig. 1. Cyclical steroid replacement regimen (E_2, oestradiol; P_4, progesterone). From Lutjen *et al.* (1986) with permission.

donation has now become a realistic means of infertility treatment for three groups of women: (i) women lacking functioning gonads because of ovarian failure or castration; (ii) women in whom standard IVF techniques have failed to harvest adequate oocytes; and (iii) women who do not wish to use their own gametes because of the risk of transmitting hereditary disorders such as Huntington's chorea. The second and third groups usually have intact ovarian function, but in agonadal women artificial menstrual cycles are required to provide a receptive endometrial environment before proceeding to gamete donation.

Pregnancy in agonadal women offers a unique model to investigate the endocrinology of early human pregnancy in the absence of interfering ovarian factors, and provides an opportunity to assess both the temporal window during which the blastocyst is able to implant, and the presence of morphological and biochemical markers of endometrial receptivity (Rogers *et al.* 1988).

This review comprises an overview of the Monash–Epworth oocyte donation programme.

Steroid replacement regimens

Women lacking ovarian function require exogenous steroid replacement to prime the endometrium in readiness for embryo transfer.

Fixed cyclical regimen ('standard' regimen)

Most groups have utilized cyclical steroid replacement, with oestradiol (E_2) administered in an incrementally increasing fashion in the follicular phase, to mimic the natural cycle (Lutjen *et al.* 1986).

Following a withdrawal bleed, oral oestradiol valerate is given, starting at a dose of 1 mg daily, increasing to 6 mg daily in mid-cycle (Fig. 1). Progesterone (P_4) is introduced on day 15 in the form of a vaginal pessary (25 mg on day 15; 50 mg on day 16; 100 mg on day 17 onwards) and continued until day 26. Thereafter, steroid withdrawal results in menstruation, and a new cycle is begun. During the second treatment cycle, patients undergo daily venepuncture to measure circulating concentrations of E_2, P_4, FSH and LH, and on day 21 (the 7th day after starting P_4 treatment) an endometrial biopsy is obtained both to confirm appropriate secretory change under the light microscope, and to assess endometrial ultrastructure (Murphy *et al.* 1987). Patients remain on cyclical steroid replacement until a donated oocyte becomes available.

Circulating E_2 and P_4 concentrations in 34 women in their second steroid replacement cycle are shown in Fig. 2. Although the fall after the mid-cycle peak of E_2 is not followed by a luteal-phase rise, the circulating concentrations are higher throughout the cycle than would be expected in a natural cycle. P_4 concentrations on day 15 and 16 are higher than those seen in the normal cycle, but the converse applies from days 22 to 26. Lower circulating P_4 concentrations after the administration of P_4 pessaries could be explained by variable vaginal absorption, for a mean peak P_4 concentration of 86 nmol/l on day 22 has been reported after treatment with 50 mg P_4 intramuscularly from day 17 (Navot *et al.* 1986).

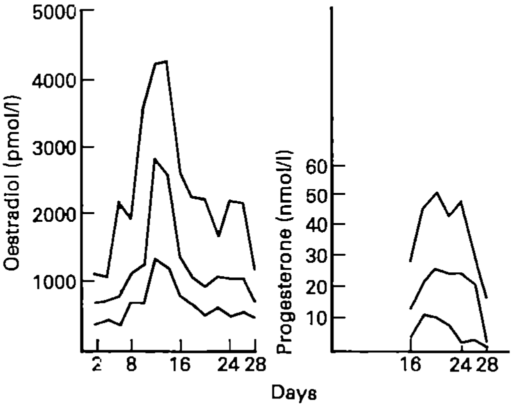

Fig. 2. Circulating oestradiol and progesterone concentrations in 34 agonadal women taking cyclical steroid replacement. Median values are shown, with the 10th and 90th centiles. From Cameron *et al.* (1988*b*) with permission

Despite supraphysiological circulating E_2 concentrations, both FSH and LH remain elevated in 70% of these agonadal women on steroid replacement. Furthermore, complete gonadotrophin suppression is not seen when P_4 is introduced. This may be due in part to the short duration of steroid administration, though FSH concentrations remained elevated in two of three women who underwent blood sampling throughout the third cycle of steroid treatment (Lutjen *et al.* 1986). The lack of ovarian inhibin may contribute to the incomplete gonadotrophin suppression (see below).

If donor and recipient cycles cannot be synchronized so that the transfer of an appropriately staged embryo can take place between days 15 and 20 of the recipient cycle (and preferably on days 17 to 19 (Navot *et al.* 1986; Rogers *et al.* 1988)), donated oocytes are usually fertilized and frozen in readiness for thawing and transfer at a later stage. Salat-Baroux *et al.* (1988) reported four pregnancies that were established in this way after 13 embryo transfers on day 14 of a replacement cycle introducing vaginal P_4 on day 12.

Constant dose, variable length E_2 regimen ('low dose' regimen)

An alternative way of overcoming the problem of donor–recipient cycle asynchrony is to extend the follicular phase of the recipient cycle and start giving P_4 on the day of, or the day before, oocyte retrieval. Asche *et al.* (1987) reported five pregnancies after seven gamete intrafallopian transfer (GIFT) procedures where follicular-phase E_2 administration was maintained at 6 mg daily from day 12 until the day of oocyte retrieval, when P_4 replacement was also started. Serhal & Craft (1987) suggested that receptivity for implantation may not be critically dependent on the dose of E_2 and P_4 used to prime the endometrium. They achieved seven pregnancies after 17 attempts at gamete (7) or embryo (10) transfer, whilst administering a constant daily dose of E_2 valerate (6 to 8 mg) for 2 to 4 weeks, with the introduction of P_4 on the day before the retrieval of donated oocytes.

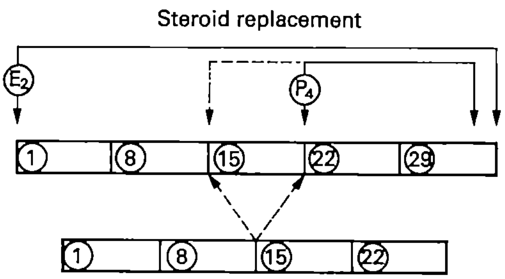

Fig. 3. Follicular-phase extension Instead of introducing progesterone (P_4) on day 15 of oestradiol (E_2) replacement in a 28-day cycle (bottom line), P_4 can be introduced on day 22, or at any time during the preceding 7 to 10 days, should an oocyte become available for donation.

We have investigated a regimen involving daily administration of 2 mg E_2 valerate supplemented with P_4 after 21 days, but starting P_4 at any time from day 10 to 21 should an oocyte become available for donation (Fig. 3).

First, endometrial development was assessed in six agonadal women after the administration of E_2 valerate, 2 mg daily for 2 weeks, supplemented with vaginal P_4, 25–100 mg for 12 days from day 15. Circulating E_2, P_4, FSH and LH were measured weekly and compared with the concentrations obtained when the six women were given steroid replacement the next month according to the 'standard' regimen depicted in Fig. 1.

Peripheral E_2 concentrations remained unchanged throughout the cycle on the constant daily dose, and were similar to expected mid-cycle concentrations in a natural cycle (1100–1800 pmol/l). Light microscopy 3 to 7 days after the start of P_4 therapy confirmed the development of normal secretory change in the endometrium, and scanning electron microscopy revealed the appearance of bulging cellular apices and irregular surface projections on endometrial cells, which is thought to be characteristic of the receptive uterus (Murphy *et al.* 1987; Rogers *et al.* 1989).

The transfer window

The creation of artificial menstrual cycles for the transfer of embryos derived from donated oocytes also permits investigation of the temporal 'window' for endometrial receptivity and successful implantation, both in terms of the endocrine milieu and ultrastructural morphology. Although the window may only be open for a few hours in mammals (Wu & Chang 1972; Seidel 1981), it may remain open for up to 3 days in primates (Hodgen 1983). An analysis of data from six oocyte donation programmes in women suggests that successful implantation may occur in the face of utero–embryonic asynchrony of ± 1·75 days (Rogers *et al.* 1988). There may be considerable variation in the steroid environment at the time of embryo transfer. However, all reported pregnancies appear to have resulted from the transfer of gametes or embryos between 1 and 4 days after the start of P_4 administration following endometrial priming with E_2 (Asche *et al.* 1987; Feichtinger & Kemeter 1985; Rogers *et al.* 1988; Salat-Baroux *et al.* 1988; Serhal & Craft 1987).

Clinical results

Twenty-two pregnancies, resulting in the birth of 13 healthy infants to date, have now been achieved in the Monash–Epworth donor oocyte programme. The results from fresh embryo (or gamete) transfers are summarized in Table 1.

There have been no statistically significant differences between the pregnancy rates obtained after transfers in either the natural cycles or in cycles primed by one or other of the two steroid replacement regimens. The five pregnancies in women on the constant E_2 ('low dose') replacement schedule were achieved following embryo transfer from day 13 to day 18 of the replacement cycle. The wider transfer window has overcome many of the problems of donor–recipient cycle synchronization, and the need to provide an incrementally increasing E_2 in the follicular phase to mimic the natural cycle has been refuted.

Two pregnancies were established with frozen-thawed embryos; in one woman the embryo was transferred in a natural cycle and she gave birth to a healthy child, the other pregnancy was established during a steroid replacement cycle but ended in miscarriage in the first trimester.

With the exception of one patient, all the women were delivered by caesarean section. There have been no perinatal deaths and no ectopic pregnancies.

Pregnancy endocrinology

Luteoplacental shift

If human chorionic gonadotrophin (hCG) is detected in the serum 12 days after embryo transfer, steroid replacement is continued until the trophoblast itself is competent to maintain pregnancy.

Circulating E_2, P_4, FSH, LH and inhibin concentrations were measured by radioimmunoassay, as described by Okamoto *et al.* (1986) and Cameron *et al.* (1988*a*), during the first trimester in four agonadal women who achieved pregnancy after oocyte donation (Figs 4 & 5). The concentrations of E_2 and P_4 rose gradually as pregnancy advanced, in the face of a constant daily dose of exogenous E_2 and P_4 (2 mg and 100–150 mg respectively).

The fact that pregnancy can be maintained by the administration of exogenous E_2 and P_4 sug-

Table 1. Results of oocyte donation and fresh gamete/embryo transfer procedures on the Monash/Epworth programme*

	Natural cycle	Steroid replacement cycle	
		Standard protocol†	Low-dose oestradiol
No. of transfer procedures*	28	54	14
No. of pregnancies			
Established	4	11	5
Rate (% transfers)	14%	20%	36%
Delivered	2	9‡	0
Ongoing	0	1	5‡
Miscarriage or anembryonic	2	1	0

*All procedures were transcervical embryo transfers except for five pronuclear stage transfer (PROST) procedures which resulted in two pregnancies. The median number of embryos replaced per transfer was 2 (range 1–4).

†For details see Fig. 1.

‡One twin pregnancy, the others were singletons

There were no significant differences in pregnancy rates natural cycle *vs* low-dose oestradiol, $P=0·09$ (Fisher's exact probability test); standard protocol *vs* low-dose oestradiol, $P>0·05$ ($\chi^2=2·43$).

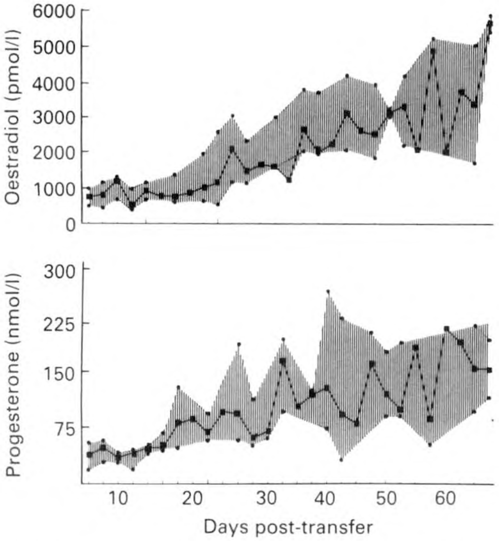

Fig. 4. Circulating oestradiol and progesterone concentrations after embryo transfer resulting in successful pregnancy in four agonadal women. Steroid administration continued for at least 72 days post-transfer in each case. Median values are shown, with the range shaded.

gests that of the ovarian hormones these two steroids alone can provide the necessary endocrine environment. Csapo *et al.* (1973) demonstrated that lute-ectomy in women, which results in early miscarriage, could be overcome by exogenous P_4. As pregnancy advances, the relative contribution of the corpus luteum to circulating P_4 concentrations falls, and the output of P_4 from trophoblast increases. The luteoplacental shift in P_4 production is usually complete about 49 days after the last menstrual period. Thereafter, the fetoplacental unit itself can provide the endocrine requirements to support pregnancy until term (Csapo & Pulkkinen 1978).

It would therefore be anticipated that to maintain pregnancy in agonadal women, exogenous steroid replacement should be required for 5 weeks subsequent to embryo transfer. In practice, although there is wide variation, most groups have continued E_2 and P_4 administration for at least 10 weeks, and the dose has either been increased and maintained at a constant level for a fixed time, or altered in relation to circulating steroid concentrations (Asche *et al.* 1987; Correy *et al.* 1988; Feichtinger & Kemeter 1985; Lutjen *et al.* 1984; Navot *et al.* 1986).

We have kept steroid replacement at a constant daily dose of 2 mg of E_2 and 100–150 mg of P_4 (vaginal or intramuscular), but the amount has been increased as necessary to maintain circulating levels within the normal pregnancy range. Steroid therapy was stopped 7 weeks after the theoretical last menstrual period, but was started again if withdrawal resulted in a marked fall in circulating steroid concentrations. E_2 and P_4 have actually been discontinued on days 85 (median; range 49–110) and 86 (49–133), respectively, following the supposed last menstrual period.

The late curtailment of exogenous steroids both by ourselves and others does not necessarily imply inconsistency with the findings of Csapo *et al.* (1973). The administration of a fixed daily dose of E_2 and P_4 will mask the timing of the luteoplacental shift (which should be heralded by an increase in circulating steroid concentrations). In addition, although a fall in E_2 and P_4 concentrations after steroid withdrawal may not inevitably result in miscarriage, most workers would exercise caution and postpone withdrawal to a later date.

Inhibin

Circulating gonadotrophin concentrations are not completely suppressed in agonadal women

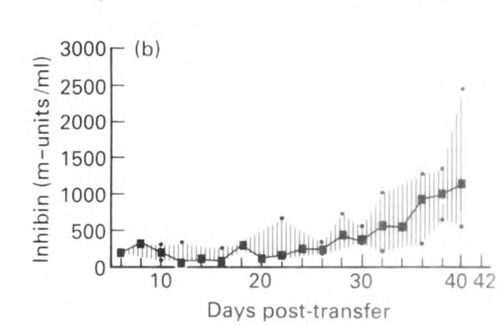

Fig. 5. Circulating FSH and LH (a) and inhibin (b) concentrations following embryo transfer resulting in successful pregnancy in four agonadal women. Median values are shown. The range for inhibin concentrations is shaded.

on steroid replacement, but fall as pregnancy establishes (Fig. 5). This could be due to the negative feedback of rising levels of E_2 and P_4, but is probably aided by the increasing production of inhibin. Although initially thought to be exclusively of ovarian origin, the presence of inhibin in pregnant agonadal women has disproved this hypothesis (McLachlan *et al.* 1987).

Conclusion

The creation of IVF techniques has allowed the development of oocyte donation programmes to manage infertility in women who cannot or do not wish to use their own gametes. The success rate for pregnancy per transfer of 20–30% compares favourably with standard IVF treatment, and is equivalent to the success rate seen in the best GIFT programmes. Furthermore the integration of oocyte donation with embryo freeze-thawing, and the development of more flexible steroid replacement regimens with an extended follicular phase have overcome many problems of cycle synchronization.

Not only is oocyte donation clinically effective, but the procedure allows the investigation of the endocrinology of early pregnancy in women. Using this model, analysis of the endocrine contribution of the trophoblast and the maternal gonad is eminently feasible, and the investigation of the endometrium, both biochemically and morphologically, is likely to reveal more of the uterine requirements for successful implantation.

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Establishment of 22 pregnancies after oocyte and embryo donation

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Summary. Donated oocytes inseminated with partner's semen or donated embryos were transferred on 95 occasions in 28 women without ovarian function and in 21 with functional ovaries. Overall, 22 pregnancies were established, 13 after the transfer of fresh embryos and nine after the transfer of frozen-thawed embryos. Eleven of the pregnancies were established in women without ovarian function and 11 in women with functional ovaries. Nine of the pregnancies were established with donated oocytes inseminated with partner's semen and 13 with donated embryos. Fifteen healthy infants were born including one set of twins; three pregnancies are progressing normally and five miscarried.

The first pregnancy established with a donated embryo in a woman with functional ovaries was reported by Trounson *et al.* (1983) and the first birth after embryo donation in a patient with absent ovaries was reported by Lutjen *et al.* (1984). Since then further pregnancies and births have been reported (Lutjen *et al.* 1985; Feichtinger & Kemeter 1985; Serhal & Craft 1987; Rosenwaks *et al.* 1986; Navot *et al.* 1986; Rozenwaks 1987; Yovich *et al.* 1987). We reported the first successful pregnancy and birth after the transfer of a frozen-thawed donated embryo (Devroey *et al.* 1987*a*; Van Steirteghem *et al.* 1987*a*).

In this report we describe the procedure and outcome of pregnancies established with donated oocytes or embryos in 28 women without ovarian function and in 21 women with functional ovaries

Subjects and methods

Between August 1984 and October 1987, 49 infertile couples were treated in our in-vitro fertilization programme using donated oocytes or embryos. Twenty-eight women had primary ovarian failure due to: gonadal dysgenesis in nine, premature menopause in nine and surgical castration in 10. Of the nine women with gonadal dysgenesis five had the following chromosomal abnormalities: homogeneous 45,X karyotype in one, an isochromosome of the long arm of the X-chromosome (46,X,i(Xq)) and an isodicentric chromosome involving the short arm and the proximal part of the long arm (46, X, i(X)) (p ter — q24 → p ter) in another; a mosaic chromosome pattern in two, one of which was a 45,X cell line in 2% of the cells, while all other cells showed a normal 46,XX chromosome complement (45,X/46,XX (2/98)) and the second was a Turner 45,X cell line in combination with an isochromosome of the long arm of the X-chromosome in 5% of the meta-

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phases (45,X/46,X,i(Xq)) (95/5); the fifth had an homogeneous 46,XY karyotype.

The 21 women with functional ovaries were treated in our donation programme because of repeatedly failed ovarian stimulation in 11, failed fertilization in the course of several in-vitro fertilization cycles in five, the presence of a genetic risk factor in four and a medical contraindication to oocyte retrieval in one. The women with genetic risk suffered from: Marfan syndrome, recurrent miscarriage, Wagner's disease and a chromosomal translocation. The mean age of the recipients was 32 years (range 23–40) in the group with absent ovaries and 34·5 years (range 25–40) in those with functional ovaries.

In couples where the man was fertile, donated oocytes were inseminated with semen of the recipient's partner and cultured *in vitro* for 48 h (Van Steirteghem *et al* 1984). If the cycles of donor and recipient were synchronous (27 procedures) the fresh embryos were transferred; if the cycles were not synchronous the embryos were cryopreserved for later use and transferred at the appropriate time after thawing (19 procedures). In couples where the male partner was also infertile, donated oocytes were inseminated with donor sperm. The embryos were either transferred fresh (28 procedures) or frozen (21 procedures). Cleaving embryos were frozen with dimethylsulphoxide as cryoprotectant (Trounson & Mohr 1985), and pronucleate embryos with a propanediol protocol (Lasalle *et al.* 1985; Van Steirteghem *et al.* 1987*b*)

Women with primary ovarian failure had steroid replacement therapy. In a cycle without embryo transfer oestradiol valerate (Progynova, Schering, Berlin) was given in combination with oral micronized progesterone (Utrogestan, Piette, Brussels) Different doses of oestradiol valerate were administered: 1 mg on days 1–5; 2 mg on days 6–8; 6 mg on days 9–13; 2 mg on days 14–17; 4 mg on days 18–26; and 1 mg on days 27–28. Oral micronized progesterone was given in a dose of 100 mg on day 14 and 300 mg from days 15 to 26. After embryo transfer we administered natural progesterone in oil (Progesteron, Sterop SV, Brussels, Federa SV, Brussels): 50 mg, intramuscularly, on day 14 and 50 mg twice daily from days 15 to 26. One woman was treated with intravaginal micronized progesterone, 200 mg on day 14 and 200 mg three times daily from day 15 onwards.

If the serum hCG became positive, the progesterone dose was increased from 100 to 150 mg and oestradiol from 4 to 10 mg daily. In the woman treated with vaginal micronized progesterone the dose was increased to 200 mg given five times per day.

In women with normal ovarian function the embryos were replaced during a natural cycle. Careful monitoring allowed the detection of the LH rise in either serum or urine. The embryos were transferred according to their developmental stage.

The endogenous LH surge was monitored in 3-h urine samples and was identified by at least two consecutive urinary LH values (U/h) higher than the mean +2 SD of the preceding values (Fig. 1).

Oocytes were donated by volunteers (n=11), patients undergoing laparoscopic sterilization (n=4) and patients undergoing in-vitro fertilization (n=6); 19 patients agreed to donate their excess fresh or cryopreserved embryos.

The donors were assessed by interview for genetic and psychological factors, all had a normal karyotype and were screened for hepatitis and AIDS. The mean age of the donors was 28·8 years (range 26–35). Ten donors were known to the recipient and 30 were anonymous.

Four different stimulation protocols were used in the donor group:

1. Clomiphene citrate (Clomid, Merrell Dow), 100 mg from day 3 until day 7 and 10 000 iu human chorionic gonadotrophin (hCG) on day 14 (Pregnyl, Organon; Profasi, Serono) in two women undergoing laparoscopic sterilization;
2. Human menopausal gonadotrophin (hMG) (Humegon, Organon; Pergonal, Serono) alone (n=1) or in association with clomiphene citrate (n=26);
3. hMG in combination with LHRH analogues (Buserelin: Suprefact; Hoechst, Frankfurt) in nine donors. Buserelin was started on day 21 or on day 1 of the cycle. The period of desensitization lasted at least 3 weeks and the start of the stimulation with hMG was extended until the artificial cycle of the recipient started (Smitz *et al.* 1987; Wildt *et al.* 1986);
4. Buserelin was administered in association with hMG from the first day of the menstrual period in two women.

In the last three protocols 10 000 iu hCG were injected according to the criteria described by Devroey *et al.* (1987*b*).

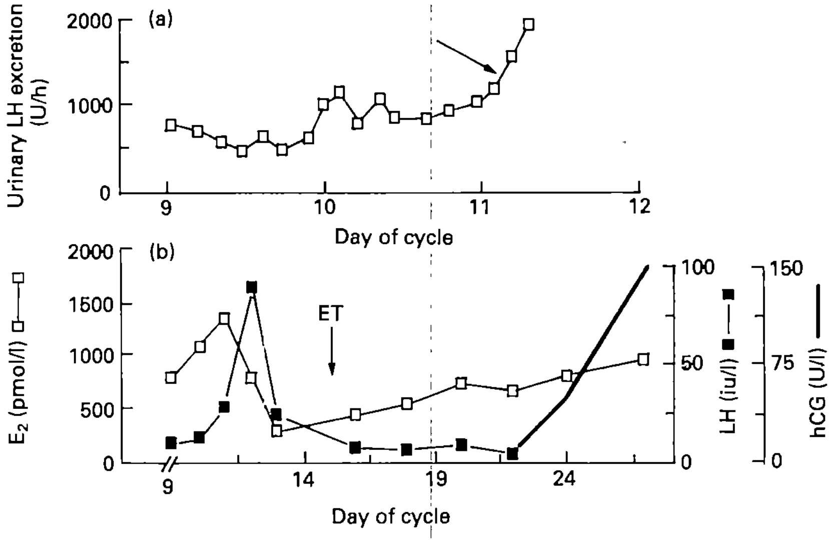

Fig. 1. Replacement of a frozen-thawed eight-cell embryo in a natural ovarian cycle. (a) Urinary LH excretion (U/h) measured in 3-h urine collection. The LH rise (↓) began on the 11th cycle day between 03.00 and 06.00 hours. (b) Serum oestradiol (E_2), LH and hCG concentration in the same patient The eight-cell frozen-thawed embryo was transferred 106 h after the LH surge; 9 days after the transfer, serum hCG became positive

Commercially available radioimmunoassays were used for luteinizing hormone (LH) (Amerlex LH RIA kit, Amersham, UK), 17β-oestradiol (^{125}I-labelled Estradiol Direct extended range radioimmunoassay kit, Radio Isotopen EIR, Switzerland) and progesterone (^{125}I-labelled progesterone Coatria, bio-Mérieux, France). Oocyte retrievals were by laparoscopy in 32 donors or under ultrasound guidance in eight (Wisanto *et al.* 1988).

The ovum donation programme was approved by the ethics committee of the hospital. After careful counselling written consent was obtained from donors and recipients (Warnock 1985; The Ethics Committee of the American Fertility Society 1986).

Results

Of the 21 women who received donated oocytes inseminated with their partners' semen 17 had primary ovarian failure and four had functional ovaries. Of the 28 women who received donated embryos 11 had primary ovarian failure and 17 had functional ovaries.

Overall, 179 oocytes were donated by 11 volunteers, 36 by 4 patients undergoing laparoscopic sterilization and 6 oocytes by 6 IVF patients; 57 embryos were excess embryos donated by 19 IVF patients (Table 1).

Embryos were transferred on 95 occasions, 55 transfers were with fresh embryos and 40 with frozen-thawed embryos.

Table 1. Number of oocytes retrieved from 11 volunteers and four women undergoing laparoscopic sterilization

	Volunteers		Laparascopic sterilization	
Stimulation regimen	No of women	No. of oocytes	No of women	No of oocytes
Clomiphene citrate	—	—	2	5
hMG	—	—	1	12
Clomiphene citrate-hMG	1	11	—	—
Buserelin-hMG	10	168	1	19

hMG, Human menopausal gonadotrophin.

Figure 2 shows the serum hormonal profile during substitution therapy with oestradiol valerate and intravaginal micronized progesterone in a cycle when two fresh embryos were transferred in a woman with Turner's syndrome. Similarly, Fig. 3 shows the endocrine profile during substitution therapy with oestradiol valerate and natural progesterone in a cycle when a four-cell cryopreserved embryo was transferred on day 17.

The pregnancies established after these 95 embryo transfers are summarized in Table 2. Twenty-two patients conceived, i.e. a pregnancy rate/transfer of 23%. These conceptions were established after a mean number of 11 substituted or natural cycles (range 1–24 cycles). Eleven pregnancies were established in women with primary ovarian failure after 53 transfers, and 11 pregnancies in women with functional ovaries after 42 transfers. Of the 22 pregnancies 13 occurred after transfer of fresh embryos and nine after transfer of cryopreserved embryos.

Nine pregnancies were established with donated oocytes inseminated with partners' semen and 13 with donated embryos. So far 14 women have given birth to 15 healthy infants. Five patients miscarried and three pregnancies are progressing normally.

Overall, 133 embryos were transferred during the 95 transfer procedures, giving a mean of 1·4 embryos per transfer. Excluding the five miscarriages the clinical ongoing pregnancy rate per transfer was 18%.

Four of the five miscarriages occurred in the 13 pregnancies established with fresh embryos and only one occurred in the nine pregnancies established with frozen-thawed embryos.

Twenty-one embryos are still cryopreserved for later use.

Discussion

In this series of 49 infertile couples requiring oocyte or embryo donation to alleviate their infertility, 22 (44%) achieved a pregnancy. The success rate of a donation programme might be improved further if the limiting factors were minimized.

The major difficulties associated with an oocyte and embryo donation programme are the availability of donated oocytes and embryos and the need for synchronizing cycles in donor and recipient.

Just as sperm donation is the only remedy for couples where the man is azoospermic, oocyte donation is the only way of producing a pregnancy for couples where oocytes are not available. Oocyte donors must be screened in the same manner as sperm donors for psychological, genetic and physical suitability and also for

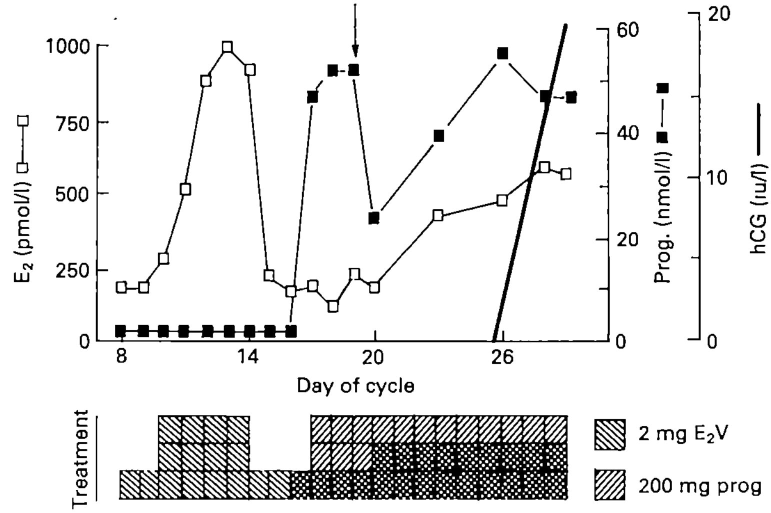

Fig. 2. Substituted cycles with oral oestradiol valerate (E_2V) and vaginal micronized progesterone (prog.) in a patient with Turner's syndrome (45XO). The arrow (↓) indicates the transfer of two fresh four-cell embryos on day 19 of the cycle (i.e. the fourth day of progesterone administration). Serum concentrations of oestradiol (E_2, pmol/l), progesterone (prog., nmol/l) and hCG (U/l) are indicated.

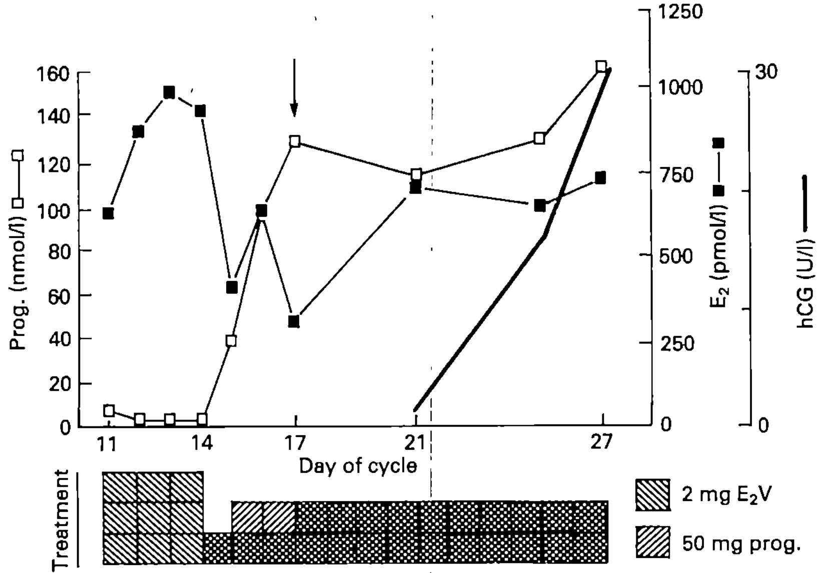

Fig. 3. Hormonal profile of an artificial cycle, substituted with oral oestradiol valerate (E_2V) and intramuscular progesterone (prog.). The arrow indicates the transfer of a four-cell frozen-thawed embryo at day 17. Serum concentrations of oestradiol (E_2; pmol/l), progesterone (prog.; nmol/l) and hCG (U/l) are depicted

infectious diseases. Like the donation of sperm, the gift of oocytes should preferably be anonymous. However, because of the complex and invasive procedures involved with donation of oocytes, donors are scarce and most couples will accept oocytes from relatives and friends (Leeton *et al.* 1986; Leeton & Harman 1986).

An important factor in the success of a donation programme is the synchronization of the ovarian cycles in donor and recipient. Donated embryos should be available at the time that the endometrium of the recipient is receptive but spontaneous synchrony is rare. There are two ways of circumventing this difficulty, first an adequate cryopreservation programme and second the combined use of GnRH analogues and hMG to stimulate the donor.

With an adequate cryopreservation programme, donated embryos can be frozen and thawed later at the time appropriate for the recipient's cycle. The present study shows that successful pregnancies can be established with the transfer of frozen-thawed embryos. Cryopreservation will also be useful where more than three fresh embryos donated by a relative are available for transfer.

As reported earlier, the combined use of GnRH analogues and hMG for ovarian stimulation provides an alternative way of synchronizing cycles in donor and recipient (Devroey *et al.*

Table 2. The establishment of 22 pregnancies with donated oocytes/embryos in 49 women

	Women with primary ovarian failure			Women with functional ovaries		
Transfer of	No. of embryos	No. of transfers	No. of pregnancies	No. of embryos	No. of transfers	No. of pregnancies
Fresh embryos	40	30	7	27	25	6
Oocytes donated	29	22	4	7	5	2
Embryos donated	11	8	3	20	20	4
Cryopreserved embryos	34	23	4	32	17	5
Oocytes donated	23	12	2	17	7	1
Embryos donated	11	11	2	15	10	4
Total	74	53	11	59	42	11

1989). The duration of hypothalamic suppression with GnRH analogues before hMG administration can be varied to match the recipient's cycle. The donor is treated with the GnRH analogues until the first day of the natural or artificial cycle of the recipient so that four- to eight- cell donor embryos beome available around day 17 of the recipient's cycle. However, it is difficult to achieve this in practice because of the variations in length of the donor's follicular phase so that these embryos can become available between days 12 and 19 of the recipient's cycle. If the recipient has no ovarian function and receives a steroid replacement therapy, the day on which progesterone supplementation is started can be adapted accordingly. For recipients requiring steroid replacement therapy, the low dose of oestradiol valerate (1 mg) can be extended and the artificial cycle will only be started the first day of the menstrual cycle of the donor. Here also progesterone administration can be started the day before the oocytes will be retrieved from the donor.

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Morphometric differences between the placental vasculature of non-smokers, smokers and ex-smokers

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Summary. The aim of this study was to determine whether cigarette smoking during pregnancy has an adverse effect upon the placenta's capacity for gaseous exchange. Using recently developed stereological techniques, in conjunction with perfusion fixation, computer-assisted measurements were made on the placentas of 15 non-smokers, 15 moderate smokers, 15 heavy smokers and 13 ex-smokers, 7 of whom stopped smoking during the course of the pregnancy. Compared with the placentas of non-smokers and of those who stopped before pregnancy, it was found that the placentas of smokers and of those who stopped after conception exhibited a reduced capillary volume fraction, and an increased thickness of the villous membrane. Although they must impair gaseous exchange across the placenta, these changes were less severe than suggested by previously published reports. Nonetheless it is clear that in order to prevent these changes women should stop smoking before conception rather than during the course of a pregnancy.

Maternal cigarette smoking during pregnancy has been known for many years to be associated with a significant reduction in birthweight (see Pirani 1978 for historical review), yet the cause for this growth retardation is still not clear. As in any other pregnancy the normal functioning of the placenta is essential for fetal well-being and so it is surprising that few quantitative studies have been performed to investigate the effects of cigarette smoking on placental structure.

On gross examination placentas from smokers appear normal (Mulcahy *et al.* 1970; Spira *et al.* 1977), and indeed the frequency of maternal infarcts is lower than that in non-smokers (Christianson 1979). At the light microscopic level there is no difference in the degree of villous maturity (Van der Veen & Fox 1982), and no excessive villous necrosis or abnormalities (Spira *et al.* 1977). Other findings have often proved inconsistent, or even contradictory. For example Lohr *et al.* (1975) reported an increased frequency of obliterative endarteritis within the villi, but this was not confirmed by Spira *et al.* (1977), Naeye (1978) or Van der Veen & Fox (1982). Equally, Spira *et al.* (1977) found an increased frequency of syncytial knots but no proliferation of the cytotrophoblast cells, whereas the opposite was the case in the study of Naeye (1978).

There is, however, some consensus amongst the authors of qualitative descriptions that placentas from smokers do display both a thickening of the trophoblastic basal lamina and a reduction in the size of the fetal capillaries (Asmussen 1977, 1980; Van der Veen & Fox

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1982; Mochizuki *et al.* 1984). These aspects of placental structure were later quantified by Van der Velde *et al.* (1983) and Van der Velde & Treffers (1985). This has led to the suggestion that the placenta's capacity as an organ of respiratory exchange is reduced in smokers, and that the fetus may suffer from chronic hypoxia as a consequence.

Recently, the structural characteristics which determine the placenta's diffusing capacity have been reappraised, and the most important factor was shown to be the harmonic mean thickness of the villous membrane separating the maternal and fetal circulations (Laga *et al.* 1973; Mayhew *et al.* 1986). Unfortunately, however, no data on membrane thickness are available for smokers' placentas. This lack of critical information, along with the introduction of perfusion fixation which has a profound effect upon the values of many structural variables (Burton *et al.* 1987), prompted us to perform the present morphometric study.

The aim was to obtain quantitative data from the placentas of non-smokers, moderate and heavy smokers. We were also interested in whether the placental vasculature returns to normal if the pregnant woman stops smoking, and if so whether there is a critical stage in pregnancy by which she must stop if this is to be achieved. Material was therefore also collected from women who had given up smoking after they learnt they were pregnant, as well as from some who had stopped just before conceiving.

Subjects and methods

Selection of subjects

The experimental design was that 15 placentas were to be collected from each of the following five groups of patients: (a) women who had never smoked; (b) women who stopped smoking shortly before conception (preconceptional stoppers); (c) women who stopped smoking during the pregnancy itself (post-conceptional stoppers); (d) women who smoked moderately (1–15 cigarettes per day); (e) women who smoked heavily (> 15 cigarettes per day).

Women who had merely reduced the number of cigarettes smoked during pregnancy were not included in the study. Potential cases were identified by inspection of the antenatal notes which were marked to alert the attention of the staff of the delivery suite

All women chosen were under 35 years of age, and were delivered of singleton fetuses at between 38 and 42 weeks gestation. Gestational age was calculated from the last menstrual period and confirmed by an ultrasound scan at 18 weeks gestation. Pregnancies complicated by hypertension, diabetes, or rhesus incompatibility were not studied, and there were no associated congenital abnormalities.

Within 24 h of the birth, each woman's smoking history was confirmed in a detailed interview. Provided the above criteria were fulfilled the first 15 placentas delivered in each group were entered into the study. Unfortunately many of the women who had declared themselves to be ex-smokers at the first antenatal visit did in fact resume smoking later in the pregnancy and thus had to be excluded. In consequence, therefore, despite prolonging the study considerably we were able to obtain only a relatively small number of reliable cases in the two ex-smokers groups, namely six and seven women in groups (b) and (c) respectively.

Prior approval for this study was obtained from the local ethics committee.

Placental preparation

Placentas were collected immediately after delivery (within 5 min) and were processed by the perfusion fixation technique described previously by Burton *et al.* (1987).

Ten blocks, 2–4 mm^3 in size, were removed from the basal region of the perfused lobule and immersed in fixative for a further 4 h. Five of these blocks were randomly selected, post-fixed in 1% osmium tetroxide and embedded in Taab resin. Sections of approximately 1 μm thickness were then cut on an ultramicrotome, stained with 1% methylene blue/azure II, and viewed under a light-microscope at a final magnification of × 1250. This technique results in a shrinkage rate of approximately 2% (Burton & Palmer 1988).

Morphometric technique

To ensure that the placentas were examined without bias, the blocks were coded, and all measurements were made by one person (G.J.B.). Eight terminal villi were measured from each of the five blocks embedded, yielding a total of 40 terminal villi per placenta. Volume fraction and surface area estimates were made by a combination of point and intersect counting, as described previously by Burton *et al.* (1987). Orthogonal intercept lengths were measured using VIDS-IV software (Analytical Measuring Systems Ltd, Cambridge) running on a Sperry (IBM-AT equivalent) minicomputer.

Values were calculated for the following variables: (1) mean villus diameter; (2) mean vessel diameter; (3) volume fractions of fetal capillary lumina (Vv cap), of stroma (Vv stroma), and of trophoblast (Vv troph); (4) arithmetic mean barrier thickness (Ta); (5) harmonic mean barrier thickness (Th) (reciprocal of the mean of the reciprocals); (6) uniformity index (UI = Ta/Th).

Statistical analysis

Taking the above measurements in turn, the five groups of patients were compared using a one-way analysis of variance (ANOVA), after first checking for homogeneity of variances. If a significant difference was detected (at $P<0{\cdot}05$), then the relation between the individual groups of patients was examined further, using Duncan's multiple range test. Pearson's correlation coefficient was calculated in order to determine whether the magnitude of any significant difference was related to the number of cigarettes smoked per day.

For the obstetric data, stepwise multiple regression was used to examine the relative effects on birthweight of cigarette smoking and a number of maternal variables such as age, parity, duration of pregnancy and maternal weight at booking.

Results

Smoking data

The mean number of cigarettes smoked per day was 9·3 (SD 4·3) for moderate smokers, and 22·2 (SD 5·5) for heavy smokers. The average preconceptional stopper smoked 17 per day before giving up on average 13 weeks before conception. The average post-conceptional stopper smoked 12 cigarettes per day before giving up on average 12 weeks after conception.

Obstetric data

Mean values for the maternal variables and for the birthweight in each category are given in Table 1. There were no significant differences in the ages of the mothers, in their weight at the first antenatal visit, or in the duration of their pregnancies. Heavy smokers were more likely to be in their second or third pregnancy, but otherwise there were no differences in maternal parity.

By contrast, the mean birthweights showed a trend towards smaller babies amongst mothers who smoked, and Duncan's multiple range test indicated that two homogeneous groups of data were possible (Table 1). There was no significant difference in mean birthweight between women who had smoked at any stage of pregnancy, but equally there was no difference in mean birthweight between non-smokers, stoppers and moderate smokers. Stepwise multiple regression analysis revealed that amongst non-smokers and smokers, of the above maternal variables only maternal weight at booking and the number of cigarettes smoked per day had a significant influ-

Table 1. Characteristics of the women in the five study groups

	Age (years)	Weight at booking (kg)	Gestational age at delivery (weeks)	Parity	Birthweight (kg)
Non-smokers (*n* = 15)	27·0 (4·4)	60·6 (9·4)	39·1 (1·1)	0·7	3·52 (0·49)
Preconceptional stoppers (*n* = 6)	27·0 (4·5)	67·2 (10·9)	40·3 (1·0)	0·2	3·61 (0·45)
Post-conceptional stoppers (*n* = 7)	24·7 (6·7)	63·2 (10·3)	40·4 (1·4)	0·6	3·44 (0·36)
Moderate smokers (*n* = 15)	26·6 (4·5)	63·2 (9·5)	39·8 (1·3)	0·6	3·29 (0·34)
Heavy smokers (*n* = 15)	26·2 (4·0)	61·7 (11·7)	39·3 (0·9)	1·3	3·09 (0·44)
ANOVA (d.f. 4,53)	*F* 0·33	0·48	2·24	3·13	2·76
	P >0·50	>0·50	>0·05	<0·05	<0·05

Results are means (SD).
Test of significance of difference between the groups used one-way ANOVA.

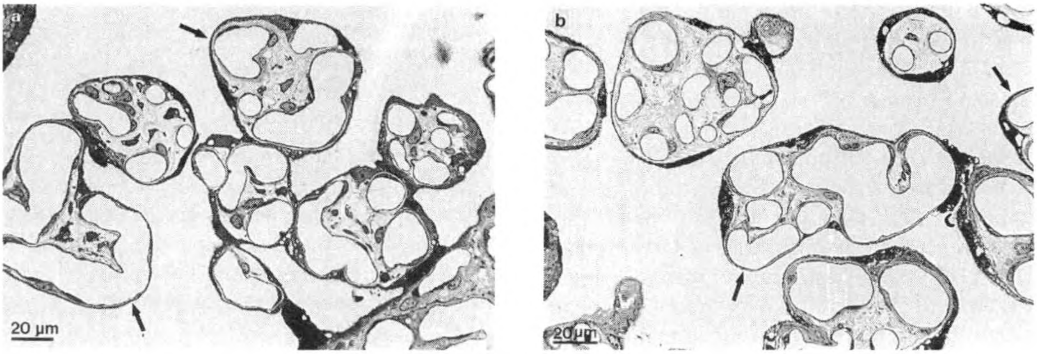

Fig. 1. (a) Terminal villi from a non-smoker's placenta following perfusion fixation. Vasculo-syncytial membranes are formed when the capillaries come into close approximation with the overlying trophoblast (arrowed). These are the principal sites of gaseous exchange. (b) Terminal villi from a woman who smoked 30 cigarettes a day throughout the pregnancy. The villi still possess large dilated fetal capillaries, with smooth luminal outlines, and there is no evidence of widespread trophoblastic damage or villitis. Vasculo-syncytial membranes are present on all the villi (examples are arrowed).

ence on the birthweight, accounting for 16% and 14% of the overall variation in birthweight respectively (regression coefficients = 0·019 and −0·017 respectively).

Placental findings

In all the blocks examined the villi appeared healthy, and there was no evidence of excessive fibrin deposition or villitis. Even in heavy smokers the fetal capillaries were well perfused, and possessed smooth regular outlines and a normal endothelium (Fig. 1). No examples of avascular villi were observed.

Morphometric data

Placental vasculature. Volume fractions are the percentages of the total volume of an organ or body occupied by specific tissues, and values for the principal components of terminal villi, namely the trophoblast, stromal tissue and fetal capillary lumina are given in Table 2. A significant difference was observed only for the capillary lumina, and the multiple range test indicated that with respect to this variable, placentas from women who had smoked at *any* stage of pregnancy were quite distinct from those who had either never smoked or not smoked since before conception. The degree of reduction in the capillary volume fraction was not significantly correlated with the number of cigarettes smoked per day ($n=45$, $r=-0{\cdot}22$, $P>0{\cdot}10$). The reduction in the capillary volume fraction observed in the post-conceptional stoppers and continuing smokers was not due to a decrease in the vascularity of the villi, since the number of capillary profiles seen was similar in

Table 2. Volume fraction for the fetal capillary lumina, trophoblast and villous stroma within the terminal villi

	Volume fraction (%)		
	Capillary lumina	Trophoblast	Stroma
Non-smokers (n = 15)	37·6 (3·7)	26·7 (2·8)	35·7 (4·0)
Preconceptional stoppers (n = 6)	38·4 (3·4)	29·8 (5·8)	38·4 (4·4)
Post-conceptional stoppers (n = 7)	31·8 (2·8)	29·8 (5·8)	38·4 (4·4)
Moderate smokers (n = 15)	32·8 (4·5)	29·4 (4·3)	37·8 (5·2)
Heavy smokers (n = 15)	33·6 (5·3)	30·7 (5·2)	35·7 (4·8)
ANOVA (d.f. = 4,53)	F 4·78	1·72	1·29
	P <0·01	>0·10	>0·10

Results are means (SD).
Significant differences between the means for the five groups of patients were tested for using a one-way ANOVA.

all five groups (Table 3). Rather, it may have been due to a reduction in the diameter of the capillaries present, for there was a trend towards narrower vessels amongst the smoking groups. The differences observed were small and not statistically significant (Table 3).

Thickness of the villous membrane. Values for the arithmetic mean and for the harmonic mean thicknesses of the villous membrane are given in Table 4. Significant differences between the groups were observed, and for both sets of measurements values were higher amongst the smokers and post-conceptional stoppers than among the non-smokers and preconceptional stoppers. Duncan's multiple range test confirmed that these two groups of patients were separate, as was the case with the capillary volume fraction. Again there was no significant correlation between the increase in thickness of the villous membrane and the number of cigarettes smoked ($n=45$, $r=0{\cdot}25$, $P>0{\cdot}05$). The harmonic mean, being based on the reciprocals of the orthogonal intercept lengths, is weighted towards the lowest values. It is therefore of particular physiological significance, since it emphasizes the contribution of the thinnest areas of the villous membrane, the vasculo-syncytial membranes. These are the principal sites of gas transfer. Dividing the arithmetic mean by the harmonic mean produces the uniformity index (UI), which is a measure of the variation in thickness of the membrane over the villous surface. The lack of any significant difference between the values of this index (Table 4) indicates that the membrane is equally variable in thickness in all the groups. There could have been no difference, therefore, in the number of vasculo-syncytial membranes on the terminal villi between placentas from smokers and those from non-smokers.

Mode of delivery of the placenta

To make certain that these observed differences were not reflecting the mode of delivery of the placenta, whether by vaginal delivery or caesarean section, a two-day analysis of variance was performed for both the capillary volume fraction and the harmonic mean thickness of the villous membrane. In view of the clear-cut distinctions indicated by the results, non-smokers and preconceptional stoppers were considered as 'non-smokers' and post-conceptional, moderate and heavy smokers were considered as 'smokers'. The main effects tested were 'smoking' and 'mode of delivery'. For the capillary volume fraction 'smoking' had a significant influence ($F=14{\cdot}7$, $P<0{\cdot}001$), whereas 'mode of delivery' did not ($F=2{\cdot}3$, $P>0{\cdot}10$). Likewise for the membrane thickness 'smoking' had a significant effect ($F=7{\cdot}9$, $P<0{\cdot}01$), whereas 'mode of delivery' did not ($F=2{\cdot}8$, $P>0{\cdot}10$).

Thus the observed differences were genuine changes associated with cigarette smoking, rather than artifactual changes induced by the different modes of delivery

Discussion

Placental vasculature

Our results suggest a less severe effect upon the vasculature than that indicated by Van der Velde *et al.* (1983) who reported a reduction in the volume fraction of the fetal capillaries from 26%

Table 3. Measures of placental vasculature in five groups of women

	Mean villous diameter (μm)	No. of vessel profiles per villous profile	Mean vessel diameter (μm)
Non-smokers (n = 15)	65·2 (4·2)	4·2 (0·4)	19·4 (1·7)
Preconceptional stoppers (n = 6)	64·7 (5·0)	3·9 (0·4)	20·3 (2·0)
Post-conceptional stoppers (n = 7)	66·3 (4·7)	4·1 (0·4)	18·7 (1·5)
Moderate smokers (n = 15)	65·6 (5·4)	4·4 (0·7)	18·1 (2·3)
Heavy smokers (n = 15)	63·8 (3·9)	4·2 (0·4)	18·1 (1·5)
ANOVA (d.f. = 4,53)	F 0·48	1·30	2·40
	P >0·50	>0·10	>0·05

Results are means (SD).
Significant differences were tested for using a one-way ANOVA.

Table 4. Arithmetic and harmonic mean thickness of the villous membrane

	Arithmetic mean (μm)	Harmonic mean (μm)	Uniformity index (UI)
Non-smokers (n = 15)	4·76 (0·56)	3·61 (0·44)	1·32 (0·16)
Preconceptional stoppers (n = 6)	4·78 (0·72)	3·61 (0·66)	1·34 (0·11)
Post-conceptional stoppers (n = 7)	5·81 (0·96)	4 63 (0·96)	1·27 (0 08)
Moderate smokers (n = 15)	5·39 (0·76)	4·14 (0·65)	1·31 (0·07)
Heavy smokers (n = 15)	5·36 (0·95)	4·16 (0·82)	1·29 (0·04)
ANOVA (d.f. = 4,53)	F 2·97	3·42	1·12
	P<0·05	<0·05	>0·10

Results are means (SD).
Significant differences between the five groups of patients were tested for using a one-way ANOVA.

in non-smokers to 15% in women smoking 20–60 cigarettes a day, a fall of nearly 50%. This discrepancy may be due partly to the much higher level of cigarette consumption in the previous study, and also to the different fixation techniques employed.

Van der Velde *et al.* (1983) used immersion-fixed material, in which the fetal capillaries are inevitably partially collapsed due to the effects of the placental transfusion. Capillary volume fractions are therefore likely to be lower than in the present study, since perfusion fixation overcomes this complication and redilates the vessels to their in-vivo dimensions (Burton *et al.* 1987). A standard pressure of 50 mmHg was used for both the smokers' and non-smokers' placentas, for at present fetal blood pressure measurements at term are not available for women who smoke. If in future the pressure is found to be significantly different then the question of under- or overdistension of the fetal vessels will have to be considered when interpreting our results.

Nonetheless, the present data indicate no decrease in the degree of vascularity of the terminal villi, in terms of the number of capillary profiles seen per villus profile. This confirms the finding of Kaltenbach (1980), and suggests there is no inhibition of growth of the capillary network as claimed by Asmussen (1977, 1980). Rather each vessel is of marginally smaller calibre, but not as contracted and distorted as depicted by some authors (e.g. Asmussen 1980; Van der Veen & Fox 1982). Since they were all working with immersion-fixed material it is possible the vascular changes they described were postpartum fixation artifacts, exacerbated by the vasoactive effects of nicotine (Lee 1987). Indeed it is difficult to equate the idea of a severely contracted capillary network with recent data indicating that the rate of blood flow in the descending fetal aorta, most of which is directed to the placenta, is almost twice as high in women who smoke as in non-smokers (Alverson *et al.* 1986).

Villous membrane thickness

The thickness of the villous membrane has not previously been measured in the smoker's placenta, even though various qualitative statements have been made regarding it (Copius Peereboom-Stegemen *et al.* 1983).

Contributing to the villous membrane are the basal laminae of both the trophoblast and the capillary endothelium, and several authors have noted an apparent increase in their thicknesses (Asmussen 1977, 1980; Van der Veen & Fox 1982; Van der Velde *et al.* 1983). Quantitative data were provided by Van der Velde & Treffers (1985), indicating an increase in thickness of the combined laminae of 0·14 μm in women who smoked more than 25 cigarettes per day. This could account for some, but not all, of the difference in overall barrier thickness observed between smokers' and non-smokers' placentas in the present study.

Possible causative factors

Most authors believe that the effects on the fetus and placenta are generally attributable to chronic hypoxia (e.g. Wilson 1971; Spira *et al.* 1977; Naeye 1978; Christianson 1979; Van der Veen & Fox 1982). This may result from underperfusion of the intervillous space, possibly due to lowering of the maternal blood pressure, or to nicotine-induced vasoconstriction of the uterine arteries. It is known for example that smoking causes not only a marked transient decrease in intervillous blood flow (Lehtovirta & Forss 1978), but also a more subtle chronic reduction (Andersen & Hermann 1984)

The situation is complex, however, for Spira *et al.* (1977) found no correlation between placental 'signs of hypoxia' (such as nuclear clumping and decreased size of the intervillous space) and increase in placental weight, which they interpreted as indicating compensatory hypertrophy. In addition their 'signs of hypoxia' were rather inconsistent, since they were seen in only 16% of smokers' placentas and in 6% of non-smokers. Equally, as Van der Veen & Fox (1982) pointed out, ischaemia may account for some of the placental changes observed, for example cytotrophoblastic hyperplasia and decreased syncytial pinocytotic activity, but by no means all. Another factor must be involved, and they implicated cadmium as the toxic agent.

It is unlikely that the placental changes observed in our study resulted from reduced perfusion of the intervillous space, for there is recent evidence showing that the harmonic mean thickness of the villous membrane is reduced, rather than increased, in situations of chronic hypoxia (Critchley & Burton 1987; Jackson *et al.* 1987). Also, the placentas of those women who had stopped smoking only a few weeks before conception were indistinguishable from those of non-smokers. It is difficult to see how any chronic damage to the uterine vasculature could have been repaired in that brief interval. Again it seems likely that the changes were caused by another agent, and cadmium appears a possible candidate.

Cadmium is rapidly accumulated in the chorioallantoic placenta following subcutaneous injections in rats (Levin & Miller 1980; Levin *et al.* 1981), and elevated levels have been measured in the placentas of smoking mothers (Miller & Gardner 1981; Van Hattum *et al.* 1981; Kuhnert *et al.* 1987). Daily injection of small doses causes both a reduction in the capillary volume fraction and an increase in villous membrane thickness (Copius Peereboom-Stegeman *et al.* 1983), findings similar to those reported here.

The ability of the placenta to accumulate cadmium so readily, and to much higher levels than other organs which are usually considered the principal site of cadmium toxicity (Levin & Miller 1980), may also explain why no difference was found between the placentas of post-conceptional stoppers and those who continued to smoke throughout the pregnancy. High placental levels of cadmium generated in the early weeks of pregnancy may have caused irreversible damage to the placental vasculature at that time, or alternatively the cadmium, being a heavy metal and so presumably slow to elute, may have persisted and affected the vessels throughout the pregnancy, even though the mother had stopped smoking. Unfortunately, placental levels are not available for such patients to clarify this point.

Significance of the findings

Placental gaseous exchange is generally held to be 'flow' rather than 'diffusion' limited (e.g. Faber & Thornburg 1983). However, of the structural characteristics which determine the organ's diffusing capacity the harmonic mean barrier thickness is by far the most influential (Mayhew *et al.* 1986). The increase in thickness of the villous membrane observed in the smokers' placentas must therefore have been detrimental to gas transfer to the fetus. Using Mayhew's model it can be estimated that in our heavy smokers category there would have been an approximately 10% reduction in the diffusing capacity compared with the non-smokers, assuming values for the other characteristics remained constant. The reduction in capillary dimensions would have had a much smaller impact on the diffusing capacity, although it may have influenced the rate of fetal blood flow, which has its own consequences. Villous surface area could increase to compensate for these changes, but for technical reasons associated with the perfusion fixation we were unable to measure it directly. Interestingly Kaltenbach (1980) reported a considerable increase in villous surface area amongst heavy smokers, both in terms of absolute values and of surface density measurements. However, it must be recognized that this finding was associated with a large increase in placental weight, an increase which has not been confirmed by many similarly sized studies (Mulcahy *et al.* 1970; Wilson 1971; Spira *et al.* 1975; Wingerd *et al.* 1976; Spira *et al.* 1977; Van der Veen & Fox 1982; Van der Velde & Treffers 1985).

On the other hand, unlike the published results for birthweight there appeared to be no dose–response relation between either the capillary volume fraction or the harmonic mean barrier thickness and the number of cigarettes consumed. This may be because of the relatively small number of placentas examined, confounded by the possible unreliability of the smokers' accounts of their smoking habits. Alternatively it may be that no such relation exists at the levels of consumption represented in our study. Previous accounts have found little or no relation between consumption and structural or physiological changes (Naeye 1978; Divers *et al.* 1981), whereas others have only observed significant changes in women smoking over 20 cigarettes a day (Mochizuki *et al.* 1984). The maximum consumption in the present study was comparatively low (30 cigarettes a day), and so it is possible that increasingly severe effects might have been seen in women who smoked more heavily.

A third possibility is that the causative agent itself shows no dose-dependent relation, and so it is relevant that whilst elevated levels of cadmium have been found in smokers' placentas, these were unexpectedly no higher in heavy smokers (20–60 cigarettes per day) than in more moderate smokers (15–20 cigarettes per day) (Copius Peereboom-Stegeman *et al.* 1983). This led the authors to suggest that although the placental tissues readily take up cadmium from the maternal circulation, there is a limit to the levels to which they can accumulate it.

We conclude, therefore, that whilst our results have shown that cigarette smoking during pregnancy does have adverse effects upon the placental vasculature, these effects are less severe than might be anticipated from previous reports. It must remain uncertain whether the consequent reduction in the organ's diffusing capacity is sufficient to restrict fetal growth, for physiological compensations may be adequate to offset any impairment in oxygen supply. Nonetheless, it is clear that in order to prevent these changes, women must stop smoking before conception, rather than during the course of the pregnancy.

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Effect of external cephalic version in late pregnancy on presentation at delivery: a randomized controlled trial

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Summary. The effect of repeated external cephalic version, performed at between 33 and 40 weeks gestation, on presentation at delivery was studied in a randomized controlled trial comprising 180 pregnant women with breech presentation. No tocolysis, analgesia or anaesthesia was used. Approximately 25% of all attempts in the study group of 90 women were successful; repeated external version resulted in cephalic presentation at delivery in 48% of patients. Spontaneous version to cephalic presentation occurred in 23 (26%) of the 90 women in the control group in whom version was not attempted, indicating a therapeutic gain from the procedure of 22%, with a 95% confidence interval of 8 to 35%. No severe complications of external cephalic version were noted. We conclude that external cephalic version reduces the frequency of breech presentation at delivery. This mainly benefits the mother because of the decrease in the number of caesarean sections and their inherent maternal morbidity.

It is generally accepted that perinatal mortality and morbidity are increased in vaginally born term-infants presenting by the breech as compared with cephalic presentations (Confino *et al.* 1985). The unfavourable perinatal morbidity associated with breech presentation at term appears to be related to vaginal delivery and has led to an increasing use of caesarean section, which has now approached 100% in some centres (Green *et al.* 1982). Although abdominal delivery may reduce fetal risks inherent in a vaginal breech delivery, maternal morbidity is increased (Collea *et al.* 1980). For this reason prevention of breech presentation at birth by means of external cephalic version has been recommended by several authors (Savona-Ventura 1986), although the effect of external cephalic version on fetal presentation at delivery remains in dispute. A number of retrospective (Savona-Ventura 1986) as well as prospective controlled (van Dorsten *et al.* 1981; Hofmeyr 1983; Brocks *et al.* 1984) studies have demonstrated a significant decrease in the rate of breech presentation at birth after external cephalic version. On the other hand, two controlled trials have failed to show any effect of external version on presentation at delivery and the authors concluded that external version anticipates spontaneous version (Mensink & Huisjes 1980; Kasule *et al.* 1985).

In view of this controversy we designed a ran-

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domized controlled trial to adduce evidence to support or refute the hypothesis that repeated external cephalic version in late pregnancy will reduce the rate of breech presentation at delivery. Within the restraints of a relatively small study, we also hoped to gain additional information regarding potential maternal and fetal risks of the procedure.

Subjects and methods

Healthy white Dutch women with an uncomplicated pregnancy of 33–40 weeks duration and a single live breech fetus were selected from the pregnant women attending the antenatal clinic of the Ikazia Hospital. The diagnosis was confirmed by ultrasound examination in all cases, and congenital malformations and oligohydramnios were excluded. Placenta praevia was also excluded, but no other placental situation was considered a reason for exclusion. Further criteria for exclusion included known uterine abnormalities, previous caesarean section, antepartum haemorrhage, suspected rupture of membranes, and fetal growth retardation. Blood group and rhesus factor were known in all women, and rhesus-negative women were screened for rhesus antibodies; rhesus-positive as well as rhesus-negative women were included in the study.

The study was designed to include 180 women with breech presentation, 90 in a study group of patients undergoing external cephalic version, and 90 in a non-treated control group. This number was chosen to be able to demonstrate a significant difference between groups with regard to presentation at delivery (alpha= 0·05 (two-sided) and beta = 0·05) assuming spontaneous version in 20% of the control group (Hofmeyr *et al.* 1986) and successful external version in 45% of the study group (Brocks *et al.* 1984).

All women gave their informed consent before being randomly allocated to the study group or the control group by means of drawing a sealed envelope. Since spontaneous version has been reported to occur more frequently in parous than in nulliparous women (Hofmeyr *et al.* 1986), nulliparae and multiparae were randomized separately to obtain an equal distribution in both groups.

Study group

This group included 40 nulliparous and 50 parous women with a breech presentation on whom external cephalic version was attempted by two experienced operators (A.W.V.C. and M.J.P.F.S.) immediately after randomization. Version was usually accomplished by the classic forward-roll technique, with the patient relaxed and in a slight Trendelenburg position. The second operator assisted by elevating the breech and manipulating the opposite fetal pole; vaginal elevation of the breech was never performed. The procedure never took more than 5 min and was discontinued if not easily accomplished or if the patient indicated discomfort. When the attempt failed or if reversion to breech presentation occurred, the procedure was repeated up to four times at subsequent antenatal visits, but never more often than twice in 1 week. Fetal heart rate was assessed by simple auscultation before and for 5 min after the procedure. No tocolytic, analgesic or anaesthetic agents were used.

Control group

This group included 39 nulliparae and 51 multiparae with a breech presentation on whom external cephalic version was not attempted All patients with a breech presentation at delivery were assessed by the attending obstetrician with regard to the mode of delivery.

Table 1. General characteristics of patients with breech presentation at entry into the study

	Study group		Control group	
	Nulliparae (n = 39)	Multiparae (n = 50)	Nulliparae (n = 39)	Multiparae (n = 51)
Age (years)	24·8 (3·8)	26·6 (4·7)	24·4 (5·2)	29·4 (4·5)
Amenorrhoea (days)	245 (7)	247 (6)	243 (17)	244 (18)

Results are means (SD)

Table 2. Results of attempts of external cephalic version

	Nulliparae (*n* = 39)		Multiparae (*n* = 50)	
Total number of attempts		90		98
Number of successful attempts		20		28
at 33–36 weeks	16		16	
at 37–38 weeks	4		9	
Successful version after two attempts	14		22	
Successful version after three attempts	5		5	
Number of patients with at least one successful attempt		17		27
Definitive success (*n*)*		17		26

*Number of patients with successful external version and a fetus in cephalic position at the time of labour.

Statistical analysis

Differences between mean values in both groups were tested with Student's *t*-test. The significance of differences between relative frequencies was assessed by means of χ^2 analysis or the Fisher test. A *P* value <0·05 was considered significant; 95% confidence intervals (CI) were calculated where appropriate.

Results

One nullipara in the study group was excluded from the analysis because she moved to another city after one successful attempt of external version. The mean age and duration of gestation of the patients upon entering the study are presented in Table 1. There were no significant differences between groups, with the exception that the parous women in the control group were older than those in the study group. The average gestational age at the time of the first attempt of external cephalic version was 35 weeks.

Success and failure of external cephalic version

A total of 188 attempts of external cephalic version was undertaken in the 89 patients in the study group. Data on overall and definitive success are presented in Table 2. Approximately 25% (95% CI 19 to 32%) of all attempts were successful, usually at 34–35 weeks, 29% in multiparae comparing favourably with 22% in nulliparae (*P*>0·05). No other specific factors associated with success or failure were identified. Spontaneous reversion to breech after successful external cephalic version occurred in five patients, three nulliparae and two multiparae In four of these patients a further attempt at external version was again successful and the fetus remained in cephalic position until delivery. Definitive success, the proportion of patients with a successful external version and a fetus in cephalic presentation at the time of labour was reached in 48% (95% CI 38 to 59%) of all patients, 44% of the nulliparae and 52% of the multiparae (*P*<0·05). Definitive success was obtained before 38 weeks gestation in 90% (95% CI 78 to 97%) and with a maximum of three attempts in all but two patients. In the study group, spontaneous version to definitive cephalic presentation occurred in none of the nulliparae and in seven multiparae with failed attempts of external version. In the control group, spontaneous and definitive version occurred in 23 women (26%; 95% CI 17 to 36%), significantly more frequently in parous women (35%) than in nulliparae (13%, *P*<0·05).

Complications of external cephalic version

There were no major complications. No rhesus antibodies were detected in rhesus-negative women included in the study, and the direct Coombs' test in cord blood was negative in the six rhesus-positive infants born to rhesus-negative mothers in the study group. A period of fetal bradycardia (approximately 100 beats/min) was observed in one patient immediately after successful version, but fetal heart rate returned to normal within 5 min. Slight painless vaginal haemorrhage that occurred 3 days after successful version in one patient disappeared spontaneously within 2 days.

Table 3. Presentation and mode of delivery

	Study group		Control group	
	Nulliparae (*n* = 39)	Multiparae (*n* = 50)	Nulliparae (*n* = 39)	Multiparae (*n* = 51)
Cephalic presentation	17	33	5	18
Successful external version	17	26	—	—
Spontaneous version	0	7	5	18
Vaginal delivery	14	33	5	17
Caesarean section	3	0	0	1
Breech presentation	22	17	34	33
Vaginal delivery	18	16	25	30
Caesarean section	4	1	9	3

Results are numbers of patients.

Presentation, mode of delivery and neonatal outcome

Table 3 shows the number of cephalic and breech presentations in both groups. Cephalic presentation was present in 56% (95% CI 45 to 67%) in the study group compared with 25% (95% CI 17 to 36%) in the control group ($P<0{\cdot}01$). The proportion of parous women with a cephalic presentation was significantly higher than that of nulliparae in both groups ($P<0{\cdot}05$).

The caesarean section rates were 9% and 14% in the study and control groups, respectively ($P>0{\cdot}05$). The caesarean section rate in patients with a breech presentation was not significantly different between the two groups (13 and 18%, respectively). There were no elective caesarean sections, the indication being arrest of labour or fetal distress during the first or second stage of labour in all cases.

Neonatal outcome is presented in Table 4; there were no significant differences between the groups except that infants born as a breech presentation in the nulliparous group had somewhat lower birthweights and were born on average 6 days earlier than babies in cephalic position in the same group ($P<0{\cdot}05$). One term infant in the control group developed severe respiratory distress shortly after having been born spontaneously in breech presentation, and died 5 h later. Necropsy showed haemorrhagic pneumonia, probably due to intrauterine infection.

Discussion

External cephalic version was successful in 25% of all attempts, a success rate that is similar to that in another Dutch study (Mensink & Huisjes 1980), but lower than that reported by most other investigators (Savona-Ventura 1986). This may be due to the fact that in our study, as well as in that of Mensink & Huisjes (1980), the procedure was immediately discontinued if it was not easily accomplished. Because in our study attempts were repeated, cephalic presentation after successful external version was eventually obtained in 48% of patients.

More important than the rate of definitive success is the net gain from the procedure, i.e.

Table 4. Neonatal outcome

	Study group		Control group	
	Nulliparae (*n* = 39)	Multiparae (*n* = 50)	Nulliparae (*n* = 39)	Multiparae (*n* = 51)
Gestation at delivery (days)	280 (12)	279 (12)	280 (12)	278 (9)
Birthweight (g)	3280 (460)	3370 (440)	3230 (430)	3390 (440)
Apgar score <7 at 5 min	1	0	0	0
Perinatal death	0	0	1	0

Results are means (SD) or numbers of infants as appropriate.

the rate of successful external version corrected for the expected rate of spontaneous version to a cephalic presentation. We found a 26% rate of spontaneous version in our control group, indicating a net gain from the procedure of 22%, with a 95% CI ranging from 8 to 35%. Most of the retrospective studies published on this subject were not controlled for spontaneous version, and for that reason the benefit from external cephalic version cannot be estimated on the basis of those data (Savona-Ventura 1986). In a partially randomized controlled trial in a group of Danish women, external version resulted in a net gain of 27% (Brocks *et al.* 1984), but much higher percentages (50–65%) can be calculated from two other controlled studies, both of them performed in a non-white population (van Dorsten *et al.* 1981, Hofmeyr 1983). In these controlled trials external version was attempted after 36 weeks, without analgesia but with the use of tocolysis. In two randomized controlled trials, one in a Dutch (Mensink & Huisjes 1980) and the other one in an African population (Kasule *et al.* 1985), external cephalic version was performed between 33 and 36 weeks gestation, or later in some cases, without tocolysis or analgesia. These studies showed no difference between the rate of breech presentation at delivery after external cephalic version and that due to spontaneous version. The lack of benefit from external cephalic version in these studies can be attributed in particular to a high percentage of spontaneous version in the control groups. Both the frequency of spontaneous version (Westgren *et al.* 1985) and the success rate for external cephalic version (Savona-Ventura 1986) have been shown to decrease progressively with advancing gestational age However, the gestational age at which the highest net gain from the procedure may be expected cannot be determined on the basis of data from the few adequately controlled studies that have been published.

In our relatively small study no serious fetal or maternal complications were noted, which supports data from other studies indicating that the risks involved in external version are extremely low when no anaesthesia is used (van Dorsten *et al* 1981; Hofmeyr 1983; Savona-Ventura 1986). Transient fetal bradycardia was noted in one of our patients; this appears to be a rather common occurrence following external version in many studies (van Dorsten *et al.* 1981; Hofmeyr 1983). The underlying mechanism may be transient fetal hypoxia due to impaired maternal blood flow to the placenta during the period of increased uterine pressure caused by manipulation (Hofmeyr & Sonnendecker 1983). For that reason we feel that the procedure should be performed in a very gentle fashion and should last no longer than 5 min. Many authors advocate performing cardiotocography before, during and after external cephalic version (van Dorsten *et al.* 1981; Hofmeyr 1983; Brocks *et al.* 1984), but the benefit of this remains to be established.

Our study shows that repeated, gentle external cephalic version performed between 33 and 40 weeks gestation reduces the rate of breech presentation at delivery. Although it may be assumed that a reduction of the number of breech presentations will also reduce the inherent perinatal risks and the caesarean section rate, these effects are difficult to assess. Only about 3–4% of all infants present by the breech at term, and although neonatal morbidity and mortality after breech delivery are three to five times higher than that associated with cephalic presentations (Chamberlain *et al.* 1975; Collea *et al.* 1978), the absolute figures have become so low in modern obstetrics that a controlled trial involving many thousands of patients would be needed to make a valid estimate of the effect of external cephalic version on perinatal outcome. The impact of external version on the caesarean section rate will depend to a large extent on the strategy of management of breech presentation. In the present study the caesarean section rate in women with a breech presentation was 16%, much lower than that reported in many other studies (Green *et al.* 1982; Savona-Ventura 1986), and the impact of external cephalic version on the caesarean section rate was low. However, in centres where caesarean section is performed more liberally in an attempt to reduce perinatal risks associated with vaginal breech delivery, a reduction of the rate of breech presentation may be expected to lead to an important decrease in the number of caesarean sections and their associated maternal morbidity (Collea *et al.* 1980).

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Circadian variations of plasma atrial natriuretic peptide in four types of hypertensive disorder during pregnancy

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Summary. Circadian variations in plasma atrial natriuretic peptide were studied, to clarify the characteristic pathophysiology of pregnancy-induced hypertension (PIH). The mean 24-h values (range) of atrial natriuretic peptide in mild and severe PIH, pregnancy-aggravated hypertension, chronic hypertension and normal pregnancy were 130·1 (97·3–207·0), 225·4 (202·8–281·8), 213·1 (183·2–249·5), 81·3 (61·8–116·1) and 77·1 (56·0–123·5) pg/ml, respectively. The values in PIH and pregnancy-aggravated hypertension were significantly higher, although those in chronic hypertension were no different from normal pregnancy. Plasma atrial natriuretic peptide showed a clear circadian rhythm with acrophase in the middle of the night, in mild and severe PIH. In the other hypertensive disorders, a circadian rhythm could not be confirmed. The results indicate that the elevated values of plasma atrial natriuretic peptide in hypertensive disorders during pregnancy relate to generalized vasoconstriction, and that the diurnal rhythm is a specific characteristic of PIH.

Human atrial natriuretic peptide, having natriuretic, diuretic and vascular smooth muscle relaxant activities, was isolated from atrial walls (Kangawa & Matsuo 1984). Recently, it was reported that plasma human atrial natriuretic peptide concentrations in pregnant women with pre-eclampsia were significantly higher than those in normal pregnant women (Thomsen *et al.* 1987; Miyamoto *et al.* 1988*a*). It is considered that the rising plasma human atrial natriuretic peptide concentrations in pregnant women with pre-eclampsia may reflect increasing peripheral resistance resulting from generalized vasoconstriction (Miyamoto *et al.* 1988*a*). However, there have been no reports of plasma human atrial natriuretic peptide concentrations in pregnant women with other hypertensive disorders.

To understand the pathophysiological characteristics of pre-eclampsia, it is important to clarify the differences in the pathophysiology between pre-eclampsia and other hypertensive disorders during pregnancy. It is well known that diurnal variations of blood pressure in pre-eclampsia differ from those in normal subjects

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(Seligman 1971). Pre-eclampsia may alter the circadian rhythm of haemodynamics. In the present study the differences in circadian variations of plasma human atrial natriuretic peptide concentrations were examined in both pre-eclamptic women and pregnant women with other hypertensive disorders

Subjects and methods

The study included 19 pregnant women with hypertensive disorders and 15 normal pregnant women between 28 and 39 weeks gestation. Hypertensive women were divided into the following four groups according to the classification by the American College of Obstetrics and Gynecology (Pritchard *et al.* 1985). Group 1 consisted of four women with mild pregnancy-induced hypertension (PIH), group 2 included five with severe PIH, group 3 was made up of five with pregnancy-aggravated hypertension, and group 4 consisted of five women with chronic hypertension. The clinical data for these four groups are shown in Table 1. The 15 normal pregnant women were put into a fifth group for this study. All women with PIH were primigravid with no evidence of renal or cardiovascular disease Mean values of blood pressure obtained for 3 months before conception in women with hypertensive disorders other than PIH, and mean values of blood pressure during the first trimester in the women with PIH are shown in Table 1. The pregnant women with chronic hypertension, who had an increase in blood pressure of 30 mmHg systolic and/or 15 mmHg diastolic over preconceptional blood pressure, were diagnosed as having pregnancy-aggravated hypertension. None of the women took any drugs before or during the study, except for iron supplement. Before the start of this study, informed consent was obtained from all participants.

All women were admitted to the Maternal Care Unit of Kyushu University Hospital at least 2 days before the study was performed. The normal pregnant women were prescribed a diet

Table 1. Clinical data on the women with hypertensive disorders

Patient no	Age (years)	Gravida/Para	Gestational age at the study (weeks)	Blood pressure (mmHg) Before pregnancy	Blood pressure (mmHg) On admission	Proteinuria (g/day)	Oedema
(1) PIH (mild)							
1	29	1/0	36	114/60*	152/90	0	+
2	30	1/0	37	124/72*	140/92	2	−
3	23	1/0	37	130/80*	150/100	1	+
4	29	1/0	39	120/60*	146/94	1	+
(2) PIH (severe)							
5	26	1/0	29	120/56*	160/112	3	+
6	26	1/0	30	132/60*	170/120	4	+
7	24	1/0	35	112/54*	170/110	3	−
8	28	1/0	35	124/62*	176/110	5	+
9	33	1/0	35	128/74*	166/116	3	−
(3) Pregnancy-aggravated hypertension							
10	35	2/1	28	146/92	170/118	2	−
11	32	3/1	30	156/90	176/112	2	−
12	32	2/1	31	150/70	170/100	3	−
13	33	2/1	32	162/90	180/110	3	−
14	34	3/2	35	164/98	180/120	2	−
(4) Chronic hypertension							
15	39	5/2	38	150/94	160/106	0	−
16	32	5/2	31	148/90	150/102	0	−
17	32	5/2	32	142/96	146/100	0	−
18	32	6/3	38	140/90	150/90	0	−
19	28	2/1	37	150/98	150/100	0	−

PIH, Pregnancy-induced hypertension.

*The values are mean values of blood pressure during the first trimester of pregnancy containing approximately 170 mEq/day of sodium, and women with PIH, pregnancy-aggravated hypertension or chronic hypertension were given about 120 mEq/day of sodium. All women remained in bed except to urinate and defecate, and slept between 22.00 and 06.00 hours.

The same examiner (S.M.) measured blood pressure every 4 h, at 02.00, 06.00, 10 00, 14.00, 18 00 and 22.00 hours, using a manual sphygmomanometer at the right brachial artery after the women had lain in the left recumbent position for 15 min or more. Simultaneously, venous blood samples were collected in chilled tubes containing 2 N ethylenediaminetetra-acetic acid and 2500 kallikrein inhibitor units of Trasylol (Bayer, Leverkusen, West Germany). The plasma was immediately separated by centrifugation at 4°C and stored at −70°C.

Plasma human atrial natriuretic peptide was measured by radioimmunoassay after extraction from 2 ml of plasma with an ODS-silica minicolumn (Sep-Pac C 18, Waters Associate, Inc , Milford, MA, USA), as described by Miyamoto *et al.* (1988*a*). The assay sensitivity was 12·5 pg/tube (100 μl), and intra- and interassay coefficients of variations were 6·9 and 7·3%, respectively.

Detection of circadian rhythms was explored by fitting cosine curves of 24-h time periods, using the cosinor analysis (Nelson *et al.* 1979). A value of $P<0{\cdot}1$ was regarded as statistically significant. Statistical analysis of the mean 24-h values and plasma values for each sampling time was by Student's *t*-test. A P value $<0{\cdot}05$ was regarded as significant.

The statistical analysis of plasma human atrial natriuretic peptide concentration used log transformed data.

Results

The mean values (range) from the 24-h mean values of plasma atrial natriuretic peptide in groups 1, 2, 3, 4 and 5 were 130·1 (97·3–207·0), 225·4 (202·8–281·8), 213·1 (183·2–249·5), 81·3 (61·8–116·1) and 77·1 (56·0–123·5) pg/ml, respectively (Table 2). The 24-h values of plasma atrial natriuretic peptide values in groups 1 (mild PIH), 2 (severe PIH) and 3 (pregnancy-aggravated hypertension) were significantly higher than those in group 5 (normal pregnancy) ($P<0{\cdot}01$), and those in group 4 (chronic hypertension) were not significantly different from those in group 5. In group 1 the mean 24-h values of plasma atrial natriuretic peptide values were significantly lower than those in groups 2 and 3 ($P<0{\cdot}01$), and there were no significant differences between groups 2 and 3.

The values of plasma human atrial natriuretic peptide at every sampling hour in each case with hypertensive disorder are shown in Table 2. The cosinor analysis of plasma atrial natriuretic peptide also confirmed a circadian rhythm fitting cosine curve with the acrophase at the middle of the night in groups 1 ($P = 0{\cdot}050$) and 2 ($P = 0{\cdot}014$). In groups 3, 4 and 5, a circadian rhythm of plasma atrial natriuretic peptide could not be confirmed using the cosinor analysis (Fig. 1). For groups 1 and 2, the acrophase (the time when the peak value is reached, theoretically) was at 23.42 hours and 00.25 hours, respectively. There was no significant difference in the acrophase between these two groups.

Mean arterial blood pressure on admission to the hospital in groups 1, 2, 3, 4 and 5 was 111·7 (SD 3·6), 131·9 (SD 3·2), 133·0 (SD 6·1), 116·7 (SD 5·0) and 65·4 (SD 8·8) mmHg, respectively. Mean arterial blood pressures for groups 1, 2, 3 and 4 were significantly higher than that in group 5 ($P<0{\cdot}01$). Mean arterial blood pressures in groups 2 and 3 were significantly higher than those in groups 1 and 4 ($P<0{\cdot}01$). Figure 2 shows the circadian variations of mean arterial blood pressure for all groups. The values were expressed as the mean per cent deviation from the mean 24-h values. In groups 1, 2 and 3 the circadian variation of mean arterial blood pressure showed a clear circadian rhythm with the acrophase at the middle of the night ($P = 0{\cdot}05$, $P = 0{\cdot}01$, $P = 0{\cdot}03$, respectively), and group 5 showed a circadian rhythm with the acrophase in the afternoon ($P = 0{\cdot}051$), using the cosinor analysis. The circadian rhythm of groups 1, 2 and 3 was opposite of that in group 5.

Discussion

It has been reported that plasma human atrial natriuretic peptide concentrations in the normal pregnant women during the third trimester of pregnancy were significantly higher than those in normal non-pregnant women (Miyamoto *et al.* 1988*a*), and that there were no significant differences in plasma human atrial natriuretic peptide during the third trimester of pregnancy (Rutherford *et al.* 1987; Miyamoto *et al.* 1988*a*). Recently, it has been reported that plasma

Table 2. Plasma human atrial natriuretic peptide values at each sampling hour and mean 24-h values

	Plasma atrial natriuretic peptide (pg/ml)						
	Sampling time						Mean 24-h values
Patient no.	02.00	06.00	10.00	14.00	18.00	22.00	
(1) PIH (mild)							
1	127·4	108·7	121·3	114·0	116·5	145·4	121·6
2	322·3	206·4	177·7	164·4	157·5	256·5	207·0
3	159·2	147·3	79·0	118·8	105·5	182·3	127·4
4	139·6	92·3	46·0	96·0	134·8	109·8	97·3
Mean	173·8	132·1	94·2	121·1	127·1	165·6	130·1
(2) PIH (severe)							
5	284·6	249·5	154·8	242·7	357·9	336·6	261·9
6	237·9	241·9	205·5	167·2	186·1	251·5	212·8
7	218·8	273·0	152·8	143·9	282·9	211·7	207·0
8	441·7	349·4	236·5	172·3	227·9	350·9	281·8
9	235·4	175·6	124·6	178·2	271·0	277·2	202·8
Mean	273·6	251·8	170·2	178·2	221·8	281·9	225·4
(3) Pregnancy-aggravated hypertension							
10	137·1	110·7	231·9	235·0	216·3	212·6	183·2
11	181·9	181·2	137·0	263·3	179·4	277·1	197·2
12	344·7	257·2	356·3	274·1	136·8	203·0	249·5
13	255·5	232·3	192·9	222·1	224·3	266·0	231·2
14	196·0	220·3	183·1	212·2	265·7	196·2	210·9
Mean	212·3	192·3	208·9	240·4	199·6	228·6	213·1
(4) Chronic hypertension							
15	85·5	60·8	73·3	143·2	59·3	88·1	81·1
16	41·0	83·7	84·4	80·2	73·5	114·7	76·2
17	58·7	60·3	65·0	68·2	42·4	84·1	61·8
18	155·6	157·1	66·0	88·8	131·4	130·9	116·1
19	92·9	43·4	58·6	139·9	61·8	126·4	79·8
Mean	78·5	73·1	68·9	99·4	68·4	106·9	81·3
Normal pregnancy (third trimester; *n* = 15)							
Mean	77·3	77·7	78·0	67·0	81·5	82·0	77·1
Range	(55·9–135·4)	(58·3–111·4)	(56·2–109·6)	(59·8–129·5)	(58·4–138·2)	(46·7–134·6)	(56·0–123·5)
Normal non-pregnant women (*n* = 5)							
Mean	40·7	43·1	44·2	52·2	40·3	44·3	44·0
Range	(26·0–71·4)	(27·1–72·0)	(31·2–68·2)	(32·3–67·4)	(29·1–53·3)	(30·0–71·0)	(29·5–66·2)

PIH, Pregnancy-induced hypertension. The mean values were calculated from log transformed values.

human atrial natriuretic peptide concentrations rose significantly in pre-eclampsia, and that the values were related to the severity of the pre-eclampsia (Thomsen *et al.* 1987). In the present study the mean 24-h values of plasma human atrial natriuretic peptide in both mild and severe PIH were significantly higher than those concentrations in normal pregnant women, and those in severe pre-eclamptic women were significantly higher than those in mild pre-eclamptic pregnancy. These results were consistent with the previous report (Thomsen *et al.* 1987). On the other hand, it remains controversial whether or not plasma human natriuretic peptide values rise in individuals with chronic hypertension. Sagnella *et al.* (1985) reported that, in patients with essential hypertension, plasma human atrial natriuretic peptide values rose, compared to those in normal subjects Larochelle *et al.* (1987), however, reported that there were no significant differences in plasma human atrial natriuretic peptide concentrations between subjects with normotension and essential hypertension. In addition, there have been no reports concerning plasma atrial natriuretic peptide values in pregnant women with hypertensive disorders. In the present study, plasma human atrial natriuretic peptide levels in women with

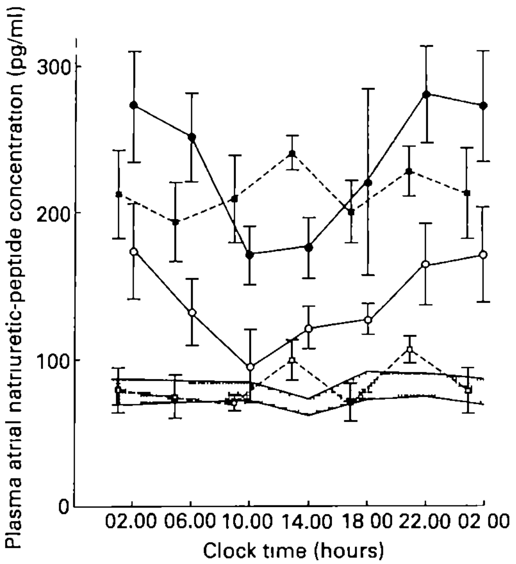

Fig. 1. Circadian variations of plasma human atrial natriuretic peptide in four different hypertensive disorders during pregnancy Shaded area shows the mean values (SE) in the normal pregnant women. ○, Mild PIH; ●, severe PIH, ■, pregnancy-aggravated hypertension; □, chronic hypertension

chronic hypertension were not significantly different from those levels in normal pregnant women. In the women with pregnancy-aggravated hypertension, plasma human atrial natriuretic peptide levels rose significantly, compared with the levels in the women with chronic hypertension. We reported previously that, using the measurement of thermal conductivity, the microcirculation in the skin is not affected by chronic hypertension during pregnancy unless complicated with pre-eclampsia, though, in severe pre-eclampsia, microcirculation in the skin was disturbed by generalized vasoconstriction (Miyamoto *et al.* 1988*b*). In addition, plasma human atrial natriuretic peptide concentrations in women with mild PIH, whose mean values of mean arterial blood pressure were the same as those in women with chronic hypertension, rose significantly. This evidence indicates that the rising blood pressure is not the principal stimulus for increasing plasma human atrial natriuretic peptide concentrations during pregnancy, and suggests that high plasma human atrial natriuretic peptide concentrations are related to the generalized vasoconstriction in pre-eclampsia.

The diurnal changes of plasma human atrial natriuretic peptide confirmed a clear circadian rhythm with the acrophase at the middle of the night in both mild and severe PIH with no significant difference. However, the circadian rhythm of plasma human atrial natriuretic peptide was not confirmed in the pregnant women with chronic hypertension and pregnancy-aggravated hypertension. Blood pressure also confirmed the circadian rhythm with the acrophase in the middle of the night in mild and severe PIH. The mechanism behind the establishment of a circadian rhythm with the acrophase in the middle of the night of plasma human atrial natriuretic peptide and blood pressure, in women with PIH, is not clearly understood. Human atrial natriuretic peptide is released from atrial walls by the increased atrial pressure or the stretching of the atrial wall or both (Lang *et al.* 1985). Therefore, circadian rhythm of human atrial natriuretic peptide accompanied by circadian ryhthm of blood pressure in women with PIH may reflect the changes in the load to the atrium caused by either changes of peripheral vascular tone or circulating blood volume. In the women with pregnancy-aggravated hypertension, plasma

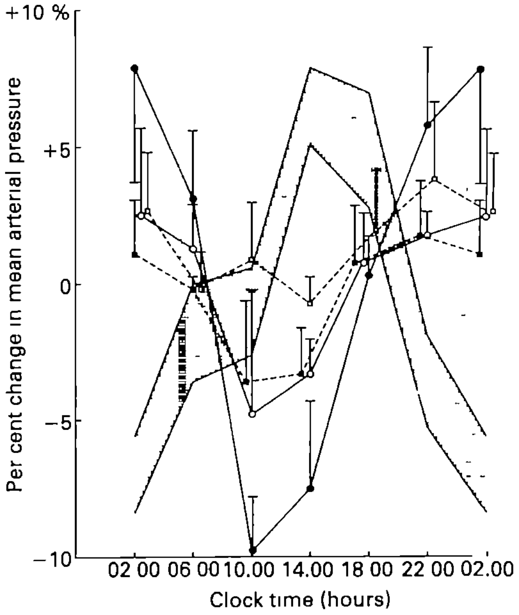

Fig. 2. Circadian variations of mean atrial blood pressure in the different hypertensive disorders during pregnancy Shaded area shows the mean values (SD) in the normal pregnant women. ○, Mild PIH, ●, severe PIH: ■, pregnancy-aggravated hypertension; □, chronic hypertension

human atrial natriuretic peptide levels rose significantly, just as they did in the women with severe PIH, but the circadian rhythm could not be confirmed. These results indicate that circadian variations with the acrophase in the middle of the night are a specific phenomenon of PIH, and suggest that the diurnal changes in the load to the atrium may be different between women with PIH and pregnancy-aggravated hypertension. The difference between PIH and pregnancy-aggravated hypertension is that women with pregnancy-aggravated hypertension already have structural changes in vascular walls (Conway 1958).

In conclusion, plasma human atrial natriuretic peptide levels rose significantly in the women with PIH and pregnancy-aggravated hypertension, but showed no significant rise in women with chronic hypertension. High plasma human atrial natriuretic peptide relates to the load on the heart due to generalized vasoconstriction, and may not be caused primarily by increased blood pressure. The clear circadian rhythm of plasma human atrial natriuretic peptide was confirmed only among the women with PIH. The circadian rhythm of plasma atrial natriuretic peptide with the acrophase in the middle of the night was a specific character of PIH. This evidence indicates that the change of plasma human atrial natriuretic peptide needs to be assessed based on the circadian rhythm of this peptide, and that diurnal haemodynamic changes are different among the four types of hypertensive disorder during pregnancy.

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Hysteroscopic endometrial ablation with the neodymium-YAG laser

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Summary. Over the past 3 years a series of patients referred to the gynaecological department at Stobhill Hospital with menorrhagia have been treated, as an alternative to hysterectomy, by endometrial ablation with the neodymium-YAG laser. The results in the first 25 patients with a follow-up of over 6 months are presented. The overall success rate was only 52%, but by increasing the power output of the laser energy used to 80 W the rate of success increased to 83%. Of the 25 patients 13 were selected for laser treatment because hysterectomy was considered unsuitable on account of obesity or medical and surgical conditions; the other 12 wanted to avoid a hysterectomy. The technique and its problems are discussed.

Endometrial ablation by laser was first reported by Goldrath *et al.* (1981). Since then various series have been reported in the American literature indicating a variety of methods with a fairly uniform degree of success. Experience in the UK seems to have been limited.

The wavelength of the neodymium-YAG laser emission (1·06 μm) has the property of passing down optical glass filaments and as such can be directed inside the body through appropriate endoscopes. Depending on the power, the energy released will heat, coagulate or vaporize tissue (Davis 1987). Consequently it has been used to destroy the endometrium in an attempt to control the symptoms of menorrhagia and so avoid hysterectomy. Goldrath (1986) has accumulated over 250 cases and reports a success rate of over 95%.

The gynaecological unit at Stobhill Hospital has been using a Fiberlase 100 neodymium-YAG laser with a Wolf operating hysteroscope (21f gauge) for the past 3 years. Follow-up in the first 25 patients has been sufficiently long to assess the technique.

Patients and methods

The patients selected were attending the gynaecology department at Stobhill because of menorrhagia, and three patients were specifically referred from the menstrual clinic at the Royal Infirmary, Glasgow, for laser ablation. One patient was referred from outside the Health Board's area.

The patients were aged from 26 to 52 years. Pretreatment assessment had included hysteroscopy and dilatation and curettage. Drug treatment had failed. The patients would normally have been considered for a hysterectomy, but were offered laser ablation instead. Ten of them were considered too obese for an easy hysterectomy, three had medical or surgical problems that made surgery hazardous, and 12 did not want a hysterectomy.

All patients understood that the treatment was experimental and that no guarantee could be given regarding effectiveness. The first 12 patients were included in a special study (Morrison *et al.* 1989) to assess the risks of fluid absorption during laser treatment, and specific consent

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Table 1. Data and outcome of endometrial ablation by laser in 25 patients (29 procedures)

Patient no.	Age (years)	Indication*	Power (W)	Time (min)	Fluid used (litres)	Outcome†	Action‡
1	30		50	80	8	Failure	TH
2	42		50	70	6·5	Failure	TH
3	44		50	80	11	Failure	Repeat
Repeat			50	80	24	Failure	TH
4	47		50	70	14	Failure	TH
5	47		50	120	24	Failure	TH
6	38	Obesity	50	70	12	Failure	TH
7	53	Long-term warfarin	50	100	11	Failure	Repeat
Repeat			80	100	31	Amenorrhoea	
8	40	Obesity	50	80	23	Failure	Repeat
Repeat			80	80	21	Minimal	
9	42		50	120	34·5	Failure	TH
10	45		60	85	52	Failure	TH
11	37	Obesity	60	80	16·5	Failure	TH
12	50	Obesity	60	90	13	Minimal	
13	34		60	90	21	Normal	Repeat
Repeat			80	50	14	Minimal	
14	47		60	95	36	Minimal	
15	43	Obesity	70	90	17	Failure	TH
16	51	Obesity	70	60	18	Minimal	
17	32		80	100	17·5	Light	
18	47	Takayasu's arteritis	80	60	12	Light	
19	26	Obesity	80	45	10	Failure	TH
20	44		80	75	24	Light	
21	34	Obesity	80	80	12	Failure	TH
22	34	Crohn's	80	75	17·5	Light	
23	49	Obesity	80	70	12	Amenorrhoea	
24	31	Obesity	80	80	25	Amenorrhoea	
25	46		80	95	14	Light	

* Indication: all patients had menorrhagia in addition to the other listed indications, patient no. 7 had continuous postmenopausal bleeding.

† Outcome indicates the nature of the menstrual flow where treatment succeeded.

‡ Action: TH, Total hysterectomy; Repeat, repeat laser ablation.

was obtained from them as required by the hospital ethics committee. The remaining patients gave normal consent for an operation.

To minimize the endometrial thickness at laser ablation, the patients were treated with danazol (Danol), 600 or 800 mg daily for 6–8 weeks before admission. Three patients who were reluctant to take danazol were treated with the LHRH analogue, buserelin, for 8 weeks before laser treatment.

The patients were admitted on the morning of the day of surgery, the operation being performed on an afternoon list. Except for the initial study group the only routine investigation was to measure the haemoglobin. The patients were not cross-matched though blood was saved for this purpose if necessary.

Laser treatment

The procedure was performed under general anaesthesia induced with thiopentone and maintained with halothane. In view of the predicted length of the procedure the patients were intubated.

The patients were placed in the lithotomy position and cleaned and draped as for a dilatation and curettage. The cervix was dilated to 9 mm and the uterine cavity was inspected with an 8-mm hysteroscope. The cavity was distended

Table 2. Outcome related to the laser power used during treatment

Power (W)	Number of procedures (n = 29)	Successful procedures n (%)
50	10	0
60	5	2 (40)
70	2	1 (50)
80	12	10 (83)

and visibility maintained using a saline or dextrose saline infusion. The infusion was run into the uterus through the hysteroscope and maintained by a peristaltic pump Two 3-litre bags of saline were used, connected to the hysteroscope via a Y tube, so that a constant infusion could be maintained throughout the procedure without interrupting therapy to change bags. The fluid escaped through the cervix around the hysteroscope and into a plastic collection bag as used by urologists.

The endometrium was ablated by placing the bare fibre-tip in contact with it and firing the laser. To minimize the thermal penetration the fibre-tip was moved during firing. Consequently the endometrium was destroyed by making parallel channels over the entire uterine surface. The fibre-tip is directed to each area of the uterus in turn. Using this contact technique the fundal and cornual areas were the most difficult to treat, as it was not easy to maintain minimal contact and move the laser safely over the surface. The walls of the uterine body were much easier to treat as the laser fibre could be laid in contact with the endometrium and a series of burns applied by retracting and advancing the laser fibre. For reasons of safety the laser was fired only while retracting the fibre.

After Lomano (1986) described his non-contact coagulation method this was adopted to treat the fundal and cornual areas. This approach requires that the laser beam is relatively vertical to the surface and not quite in contact with the endometrium. Lomano (1986) used a distance of 5–10 mm, and Daniell *et al.* (1986) attempted to keep the fibre 2–4 mm from the endometrial surface. The firing of the laser causes blanching and coagulation of the surface. This technique is not suitable for the lateral walls where the beam can only approach the surface tangentially. Consequently, the final approach to laser ablation has been a combination of non-contact coagulation at the fundus and contact ablation on the body walls.

The treatment was considered complete when all the uterine surface had been ablated down as far as the internal os. Often this point was not easy to identify, especially as visibility in this region was difficult to maintain. Throughout the procedure the quantity of fluid instilled was recorded and the fluid flowing out of the cervix was collected and measured. A significant discrepancy would indicate that fluid was being absorbed into the circulation. The procedure was completed by gently curetting the cavity. All the patients were discharged within 48 h of treatment.

Results

The 25 patients who have been treated were between 26 and 53 years of age (mean 41 years) and follow-up has varied between 6 and 30 months Four patients were treated a second time. In all, 29 procedures were performed; the data are shown in Table 1. Twelve patients have required a hysterectomy because of menstrual problems persisting after treatment.

Three patients have had no bleeding since treatment, five have minimal spotting and five have a light menstrual loss lasting 2 or 3 days. Thus, 13 of the 25 women (52%) have benefitted from laser treatment and have avoided a hysterectomy (Table 1).

The mean age of the women in whom treatment succeeded was 43 years, and in the failed group the mean age was 40 years; there was no significant difference in mean age between the two groups ($P>0{\cdot}05$, Mann–Whitney *U*-test).

In an attempt to improve the success of the procedure the power output of the laser was increased during the study up to 80 W.

Analysing the results according to the laser power used shows that the success of the technique was much greater at higher powers (Table 2). Treatment is now given at 80 W. Of the 12 procedures using 80 W (including three retreatments) only two have failed, a success rate of 83%.

Problems and complications

During the procedure the fibre-tip becomes coated with debris and this causes heating and distortion of the fibre. Consequently the power of the escaping beam is greatly attenuated. The fibre has to be changed and cleaved frequently during the procedure.

The procedure is inherently slow; the time taken ranged from 45 to 120 min (Table 1).

In this series the quantity of fluid used to irrigate the uterus has been high (Table 1). The risk of fluid overload and pulmonary oedema was first observed by Goldrath *et al.* (1981) and we examined this problem in our first 12 patients (Morrison *et al* 1989). Only one patient during 12 procedures had this complication, which was quickly reversed with diuretics. Bleeding has not been a problem during or immediately after the procedure.

One patient developed lower abdominal pain associated with a foul vaginal discharge, which a speculum examination showed to be coming through the cervix. An intrauterine infection was diagnosed and quickly controlled with antibiotics.

A small number of haematometra have been reported (Goldrath 1986), but this has not occurred in this series.

Comment

After the failure of conservative therapy, hysterectomy has been the mainstay of treatment for menorrhagia for many years. Ablation by laser is the first technique to challenge the supremacy of the knife. Experience in America has been much greater than in Europe and there are several centres offering treatment and training. Goldrath (1986) has reported on his experience, which is 10 times greater than my own, and he claims a 96% success rate. No doubt the expense of the equipment and its installation and the difficulty and slowness of the procedure plus the strict safety regulations have limited its acceptance in the UK (Davis 1987). The American surgeons with experience of this technique quote shorter treatment times (Goldrath 1986; Lomano 1986). A non-contact method speeds up the procedure, but sacrifices some control of symptoms (Loffer 1987). Contact laser ablation is slower but is more likely to produce amenorrhoea. One of the main difficulties is to maximize the effect on the uterine surfaces where the laser beam strikes tangentially. Despite the flexibility of the fibre it cannot be turned adequately in the narrow confines of the relatively undistensible uterus.

Local endometrial ablation offers advantages to the patient. The time spent in hospital is reduced (in the USA patients are treated as day cases (Loffer 1988)) and the patient is back to normal within 3 weeks. Most women appreciate the control of symptoms without complete loss of their periods. Despite the initial costs of establishing a service for endometrial ablation by laser, the savings achieved by reducing time in hospital could appeal to health managers

Although Mosely *et al.* (1987) have shown that there is minimal conduction of heat to the serosal surface of the uterus, the author remains concerned about the safety of the procedure. It can be difficult to maintain visibility unless adequate flow rates of saline are maintained. The laser fibre is relatively sharp and can easily penetrate the soft uterus. The laser should *never* be fired while the fibre is advanced. Great care must be taken to watch the fibre-tip at all times.

A microchip camera system (Wolf CCD Endocam 5370) attatched to the hysteroscope is now used in our department. The operator can watch the procedure on a monitor. This allows greater accuracy of treatment, is far more comfortable than squinting down an endoscope for over an hour, and increases the interest for the other personnel in theatre. It is probably essential to maximize the safety of the operation.

The large volumes of fluid used in this series may reflect the use of a peristaltic pump and a single-channel hysteroscope. Goldrath *et al.* (1981) stated that with experience he was using between 2 and 3 litres per procedure. Most of the other American series available for review have not noted the amount of fluid used during treatment although Lomano (1986) reported that an average of 2160 ml was absorbed during the procedure.

If infusion systems are used it is best to rely on a two-channel system putting the pump into the outflow so diminishing the risk of raising the pressure within the uterus. This is the system we are currently assessing.

Patients in whom plasma volume expansion would be dangerous due to their medical condition are not suitable for endometrial ablation by laser because of the risk of fluid infusion.

Baggish & Baltoyannis (1988) described a new approach using Hyskon (32% Dextran 70) and a treble-channel hysteroscope With this method he was able to restrict the amount of fluid infused to no more than 700 ml, and only one of his 14 medically high-risk patients required a hysterectomy for failed therapy.

Hysteroscopic endometrial ablation by laser is a difficult procedure and has not yet proved its value. It may well represent a phase in the development of endoscopic alternatives to hysterectomy. The next step is to compare laser ablation with electro-diathermy resection (DeCherney & Polan 1983).

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Uterine activity during spontaneous labour after previous lower-segment caesarean section

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Summary. Uterine activity was measured in three groups of labouring women who previously had a caesarean section (CS): group A included women with a previous elective CS before labour or in the early latent phase of labour and no previous vaginal delivery; group B included women with a CS in the active phase of labour and no previous vaginal delivery; group C included women with a CS and a vaginal delivery either before or after the abdominal delivery. The active contraction area profiles in the three groups were compared with those of matched control groups of nulliparae and multiparae without a uterine scar. Group A had a uterine activity profile similar to that in control nulliparae and significantly higher than that in control multiparae. The uterine activity in group B was less than that in matched nulliparae but was similar to that in matched multiparae. Group C had significantly less uterine activity than matched nulliparae but a similar profile to that in the matched multiparae. Progress of labour into the active phase in the previous pregnancy reduces the uterine activity profile in subsequent labour. Women who had had a vaginal delivery either before or after the CS (group C) exhibited uterine activity profiles similar to multiparae, suggesting that an intact scar did not affect the uterine function.

Craigin (1916) introduced the concept 'once a caesarean, always a caesarean', when the low transverse uterine incision was not widely practised and modern anaesthesia, blood storage techniques and antibiotics were not available. Subsequently, many authors (Gibbs 1980; Eglinton *et al.* 1984; Silver & Gibbs 1987) have reported 63 to 78% success rates of vaginal delivery in women with previous scars with little danger to the mother or fetus. In spite of such reports, many obstetricians are reluctant to allow a trial of labour in such cases because of difficulties in adequately assessing the uterine activity and the integrity of the scar. Uterine activity profiles according to parity associated with satisfactory progress of labour and vaginal delivery in parturients without a uterine scar have been reported previously (Gibb *et al.* 1984; Arulkumaran *et al.* 1984), but little is known about the power of uterine contractions expressed as uterine activity integral (the sum total of area under contractions above the baseline in a 15-min period) in women with a uterine scar.

Women who have had a caesarean section

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(CS) constitute a special category. Those delivered by CS in their first pregnancy at term after little or no labour will be technically multiparae but the uterine activity in a subsequent labour may be similar to labour in nulliparae. It may be postulated that a nullipara delivered by CS in the late first stage of labour or a multipara delivered vaginally before or after a CS should behave like a multipara in subsequent labours but this has not been studied quantitatively. We therefore investigated uterine activity profiles in different groups of women with a previous scar using a transducer-tipped intrauterine catheter and compared them with women with a cephalic presentation but without a previous CS scar.

Patients and methods

Women who had had a previous lower-segment CS and in whom a decision was made to allow a trial of scar were recruited. The study was confined to those with a cephalic presentation admitted in spontaneous labour and who progressed normally in labour with a rate of cervical dilatation of ≥1 cm/h (alert line) or within a line drawn 2 h to the right of such a line (action line) on the partogram, resulting in an unassisted vaginal delivery of an infant in good condition. The uterine activity of women who had slow progress of labour and who needed augmentation of labour is reported by Arulkumaran *et al* (1989). The women who had normal progress of labour were divided into three groups: group A included those who had had a CS electively or in the early latent phase of labour and no previous vaginal delivery; group B included those who had had a section in the active phase of labour and no previous vaginal delivery; group C included those who had had a section and also a previous vaginal delivery.

In the active phase of labour when the cervix was effaced and at least 3 cm dilated, the membranes were ruptured artificially. A solid transducer-tipped Gaeltec (Sonicaid Ltd, Chichester, UK) catheter was introduced through the vagina and cervix into the uterine cavity after calibration with a Sonicaid FM3R or FM6 fetal monitor as instructed in the Sonicaid operating handbook. The fetal heart rate using a scalp electrode and the intrauterine pressure were monitored continuously. Uterine activity was quantified on-line with a Sonicaid Uterine Activity Integrator module incorporated into the traditional fetal monitor. Vaginal examinations were made every 2–3 h to assess the progress of labour and to relate the uterine activity value to cervical dilatation. Pethidine, 75–100 mg, was given intramuscularly every 4–6 h for analgesia; epidural analgesia was not used.

The women were nursed in the left lateral position and monitoring was continued until full dilatation of the cervix when the catheter was removed. The dorsal position was adopted when the bearing down sensation was experienced. Neonatal condition was assessed by Apgar scores at 1 min, 5 min and by umbilical cord artery blood pH at delivery.

The profiles of uterine activity values were analysed collectively in relation to cervical dilatation. Centiles were derived for each cervical dilatation. Median levels were also derived for the whole labour from 3 to 9 cm. Uterine activity profiles of controls matched for height, birthweight and rate of labour progress were obtained from nulliparae (N1, N2 and N3 for groups A, B and C respectively) and multiparae (M1, M2 and M3 for groups A, B and C respectively) admitted in spontaneous labour with a cephalic presentation and satisfying the other conditions of the study except a previous CS scar. The obstetric characteristics and neonatal outcomes in groups A, B and C were compared with each other and with those in their respective control groups using χ^2-test. The cervical dilatation specific uterine activity profiles were compared using the Mann–Whitney *U*-test. The median cumulative uterine activity needed to achieve full dilatation from a given cervical dilatation was calculated for each of the study groups and their controls. The cumulative uterine activity of the study groups was compared with the respective median cumulative uterine activity of the controls using the Mann–Whitney *U*-test.

Results

The mean age in the different groups ranged from 27·1 to 29·2 years and the mean gestational age at delivery ranged from 38·7 to 39·6 weeks. The means did not differ significantly between study groups and controls. The mean height of the women and the neonatal outcome in the different groups are shown in Table 1. The neonatal outcomes judged by Apgar scores at 1 and 5 min and umbilical cord artery blood pH values were similar. None of the babies had a 1-min Apgar score <5, a 5-min Apgar score <7 or cord

Table 1. Patient characteristics and neonatal outcome

Patient group	*n*	Height (cm) Mean (SD)	Cord artery pH Mean (SD)	Birthweight Mean (SD)
A	21	154·3 (5·2)	7·30 (0·07)	3240 (324)
N1	21	155·2 (3·4)	7·32 (0·06)	3136 (289)
M1	21	154·6 (4·2)	7·31 (0·04)	3217 (391)
B	22	153·2 (4·7)	7·30 (0·06)	3120 (286)
N2	22	155·6 (3·8)	7·28 (0·04)	3240 (318)
M2	22	154·8 (4·2)	7·31 (0·05)	3192 (340)
C	14	152·4 (6·4)	7·31 (0·05)	3225 (345)
N3	14	155·2 (3·7)	7·32 (0·06)	3184 (367)
M3	14	155·0 (3·7)	7·33 (0·04)	3218 (424)

Group A:	Patients who had a previous lower-segment CS electively or in the latent phase of labour but no previous vaginal delivery
Group N1:	Control group of nulliparae for group A.
Group M1:	Control group of multiparae for group A
Group B:	Patients who had a previous lower-segment CS in the active phase of labour but no previous vaginal delivery
Group N2	Control group of nulliparae for group B.
Group M2:	Control group of multiparae for group B
Group C:	Patients who had a previous lower-segment CS but had a vaginal delivery prior to or after that event
Group N3:	Control group of nulliparae for group C.
Group M3	Control group of multiparae for group C

artery blood pH <7·15. There was no significant difference in the parity distribution and in birthweights between the study groups and their respective controls.

The median uterine activity values in group A and the corresponding control groups, N1 and M1, are shown in Fig. 1. Considering the uterine activity at different cervical dilatations, group A behaved like nulliparae except at 3 or 4 cm dilatation, the uterine activity levels were significantly higher than those in control multiparae except at 3 and 4 cm dilatation, suggesting that the uterus behaves more like in a nullipara.

The women in group B exhibited similar uterine activity profiles as were found in the control multiparae (M2) but lower activity than in the control nulliparae (N2) except at 8 and 9 cm dilatation (Fig. 2).

The women in group C had uterine activity levels similar to those in the control multiparae (M3) but significantly lower levels than in the control nulliparae (N3) except at 8 and 9 cm dilatation (Fig. 3). In all groups the activity profiles tend to show a steep rise in the late first stage of labour The overall median activity (3–9 cm) in the three groups with a previous CS was between 1035 and 1320 kPas/15 min.

Women were admitted at various cervical dilatations in labour. Cumulative uterine activity needed to dilate the cervix was calculated from a given dilatation to full dilatation in all groups (Table 2). Similar values were derived for the control nulliparous and multiparous groups. There was a declining trend from group A to C in the cumulative uterine activity needed to achieve full dilatation from a given dilatation. The overall cumulative uterine activity of group A from a given cervical dilatation to full dilata-

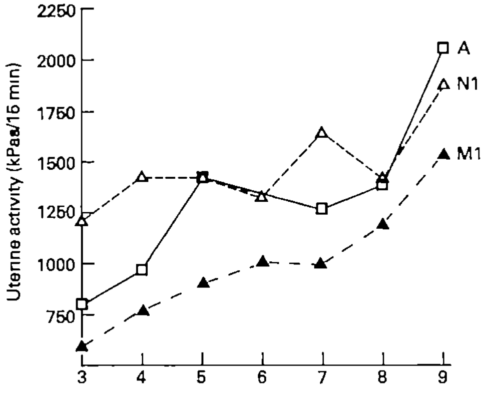

Fig. 1. Cervical dilatation specific median uterine activity values of group A compared to control nulliparae N1 and control multiparae M1.

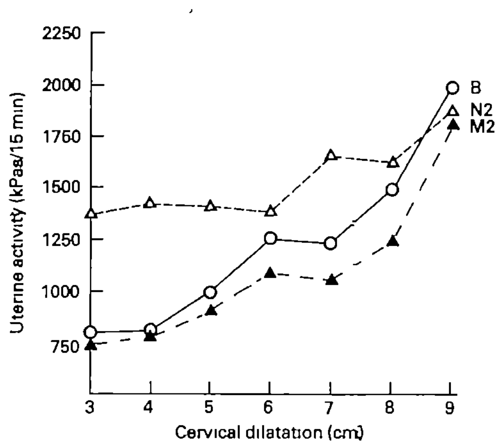

Fig. 2. Cervical dilatation specific median uterine activity values of group B compared to control nulliparae N2 and control multiparae M2.

tion was not different from that in control nulliparae but significantly higher than that in control multiparae. Similar findings were observed with group B. Group C had cumulative uterine activity like that in the control multiparae. The overall median cumulative uterine activity for the whole labour did not differ significantly between groups A and B but was higher than that in group C (A *vs* C $P = 0{\cdot}018$, B *vs* C $P = 0{\cdot}035$). Uterine rupture did not occur in any of the study groups.

Discussion

The increasing use of caesarean section is a matter of concern in many countries. Recent reports from the UK (Yudkin & Redman 1986) and the USA (Gilstrap *et al.* 1984) have suggested that dystocia, previous CS, breech presentation and fetal distress are the major contributory factors. The NIH consensus statement (Consensus in Medicine 1981) suggests that this trend may be stopped or reversed while maternal and fetal outcome continue to improve. To achieve such objectives each factor should be studied. This paper assesses the uterine function in spontaneous normal labour in those women who had a previous lower-segment CS scar.

Integrity of a uterine scar is difficult to assess. For a given scar the force exerted on the scar may be better represented by the active contraction area than the frequency of contractions. In routine clinical practice, uterine contractions are monitored by clinical palpation and by external or internal tocography. The first two methods record the frequency accurately, the duration approximately but the amplitude of the uterine contractions poorly. The use of an intrauterine catheter provides accurate information about these elements and enables the uterine activity to be computed as the area under each contraction above the baseline, that is the active contraction area. On-line computation of uterine activity will show whether a patient has levels of activity known to be associated with acceptable progress of labour (Steer *et al.* 1984). We have studied the uterine activity levels associated with acceptable progress of labour in women with a previous CS. Though the use of intrauterine catheters for managing labour in women with a previous scar has been reported, the uterine activity associated with normal labour progress has not been quantified (Flamm *et al.* 1984).

The cervical dilatation specific uterine activity profile in group A was similar to control nulliparae and higher than control multiparae. This might be expected as the women in group A had not experienced full labour in their first pregnancy and would not have had cervical effacement or dilatation. Women in group B showed a cervical dilatation specific uterine activity profile of control multiparae. This may be because these women had previously undergone the process of cervical effacement and dilatation to the active phase of labour. The women in group C who had had a vaginal delivery showed a uterine

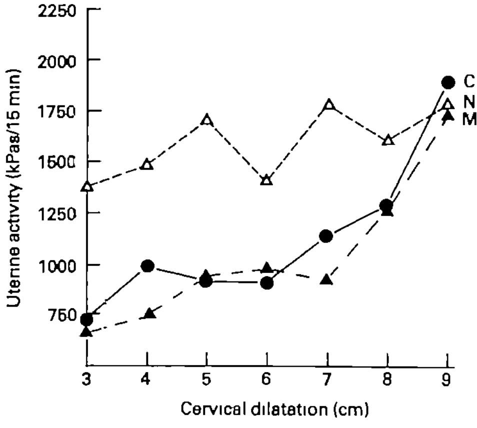

Fig. 3. Cervical dilatation specific median uterine activity values of group C compared to control nulliparae N3 and control multiparae M3

Table 2. Median cumulative uterine activity in groups A, B, C, control nulliparae and control multiparae from a given dilatation to full dilatation

Patient group	Cumulative uterine activity (kPas) over cervical dilatations (cm)							
	3–10	4–10	5–10	6–10	7–10	8–10	9–10	Overall
A	19 480	17 073	14 643	12 072	9795	6778	4070	9830
	(5)	(12)	(14)	(20)	(19)	(20)	(21)	(111)
N1	15 067	14 946	12 440	11 196	9350	7500	5000	9340
	(11)	(11)	(16)	(16)	(20)	(19)	(20)	(113)
M1	10 693	7395	7284	5601	4369	2980	2073	4454
	(8)	(14)	(16)	(13)	(17)	(17)	(20)	(105)
B	16 218	14 577	12 085	10 550	7875	6225	3524	8790
	(12)	(16)	(18)	(17)	(19)	(21)	(22)	(125)
N2	16 458	13 550	12 002	11 082	9219	7219	4422	8642
	(8)	(12)	(14)	(16)	(19)	(21)	(21)	(111)
M2	12 283	9423	9236	6090	4803	3748	2216	6446
	(10)	(15)	(18)	(19)	(18)	(20)	(22)	(122)
C	13 825	8969	9773	9836	7747	6108	2956	7280
	(6)	(9)	(12)	(14)	(14)	(14)	(14)	(83)
N3	15 425	14 946	10 031	9939	6972	5242	2813	8403
	(6)	(9)	(10)	(10)	(13)	(13)	(13)	(74)
M3	10 600	7473	7094	5254	4190	3682	2073	5290
	(6)	(11)	(11)	(12)	(9)	(12)	(14)	(75)

The number in parenthesis indicates the number of 15-min observations from which median cumulative uterine activity was calculated.
For description of groups see Table 1.

activity profile almost similar to control multiparae. In our study the cumulative or total uterine activities of groups A and B were similar to those in control nulliparae but higher than in control multiparae or in group C which may be attributable to the difference of previous vaginal delivery in the latter groups. The median values of cumulative uterine activity for cervical dilatation from 3 to 10 cm ranged from 14 000 to 20 000 kPas in the three groups A, B and C.

When cervical dilatation specific median uterine activity profiles of groups A, B and C were compared the difference was minimal and was observed only from cervical dilatations of 5 and 6 cm. Based on these findings women with a lower-segment CS scar, who progress satisfactorily in labour, have uterine activity values between 1000 and 1300 kPas/15 min. Cephalopelvic disproportion should be suspected if, despite such uterine activity, satisfactory progress in labour is not achieved in 3–4 h and if the cumulative uterine activity has exceeded 20 000 kPas. Further prolongation of labour or augmentation of labour with oxytocics will increase the cumulative uterine activity with an increased possibility of scar dehiscence.

In all groups there was a steep rise of uterine activity in the late first stage of labour which was maintained in the second stage of labour. Such high activities for long periods may not be advisable in the presence of a uterine scar. This supports the clinical practice of well-timed prophylactic forceps delivery in women with a previous scar where there is a likelihood of undue delay in the second stage of labour.

In current obstetric practice women with a previous abdominal delivery frequently have a trial of labour in their subsequent pregnancy. There is no precise method of assessing the integrity of the uterine scar. However, the force applied on the scar may be adequately assessed by measuring the uterine activity. We have described cervical dilatation specific uterine activity and cumulative uterine activity values in women with previous lower-segment CS scars. The results show that labour in the first pregnancy that progresses to the active phase of the first stage reduces the force exerted on the scar in labour in the subsequent pregnancy and is more similar to labour in multiparae than in nulliparae. An intact scar did not influence uterine activity if the patient had had a previous vaginal delivery.

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Oxytocin augmentation in dysfunctional labour after previous caesarean section

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Summary. Uterine activity was quantified in women with a previous caesarean scar and a slow progress of labour who needed oxytocin augmentation. Of the 63 women 49 (78%) progressed well (mean cervical dilatation rate of 1·5 cm/h) and were delivered vaginally. Fourteen women had slow progress of labour (0·3 cm/h) and were delivered by caesarean section despite adequate and similar augmented uterine activity to that in the women who were delivered vaginally. Those who were delivered by caesarean section had a significantly higher mean maximum dose of oxytocin and a longer period of augmentation. All caesarean sections were for cephalopelvic disproportion and the mean birthweight of babies born by caesarean section (3598 g) was significantly higher than that of babies born vaginally (3230 g). Satisfactory rate of cervical dilatation in the presence of optimal uterine activity is predictive of favourable outcome when oxytocin is used for dysfunctional labour after previous caesarean section.

Many centres allow a trial of labour in women with a previous lower-segment caesarean section (CS) scar if no cephalopelvic disproportion is suspected, but terminate the trial if labour is dysfunctional. Clinicians are reluctant to augment labour even though the risk of scar rupture is reported to be small if progress of labour is satisfactory in response to oxytocin (ACOG 1985; Silver & Gibbs 1987; Flamm *et al.* 1984). One reason is the difficulty in assessing prospectively the integrity of the scar because diagnosis of scar rupture is possible only after the event. Another is the difficulty in determining whether the cause of unsatisfactory progress of labour is poor uterine contractions or cephalopelvic disproportion.

In previous studies from this institution uterine activity profiles observed in spontaneous normal labour in patients with and without scars have been reported (Gibb *et al.* 1984; Arulkumaran *et al.* 1989). Uterine activity profiles in women with scars and abnormal labour have not been described but would be of interest. In the present investigation the obstetric and labour characteristics and the pre- and post-augmentation uterine activity profiles of patients who had a slow progress of labour with a previous CS scar were studied. The observations in patients who were delivered vaginally were compared with those who had CS for poor progress of labour despite adequate augmentation.

Patients and methods

Patient selection, study criteria and methods have been described previously (Arulkumaran *et al.* 1989). The present study describes women who had abnormal progress of labour. When the progress of cervical dilatation crossed the action line oxytocin was given intravenously at a rate of 2 mU/min. The rate was increased every 30 min using a peristaltic infusion pump (IVAC Corpor-

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ation, Sandiego, USA) to produce infusion rates of 2, 4, 6, 8, 10, 12, 16, 20, 24 mU/min until the frequency of uterine contractions was one in every 2 to 2·5 min. Women who needed a caesarean section for reasons other than failure to progress (e.g. fetal distress, cord prolapse) were excluded from the analysis.

Each patient had a computerized coding sheet in which age, height, parity, maximum oxytocin infusion rate, progress of labour, mode of delivery, indication for operative delivery, Apgar scores at 1 and 5 min, and whether the newborn was intubated or admitted to the neonatal unit were recorded. The frequency, amplitude and uterine activity represented by the active contraction area profile every 15 min (the uterine activity integral or UAI) were recorded. The mean of these values for 1 h preceding augmentation and the mean values obtained for 1 h when the maximum dose rate of oxytocin was achieved were calculated. The values obtained from those who had a satisfactory progress of labour (>1 cm in 3 h) and an unassisted vaginal delivery were compared with those who had an unsatisfactory progress of labour (<1 cm in 3 h) and a CS for failure to progress. Student's *t*-test (two-tail) was used for statistical analysis.

Results

The study group consisted of 63 women of whom 49 (78%) were delivered vaginally and 14 (22%) had a CS for failure to progress despite adequate uterine activity. The obstetric and labour characteristics of these two groups are given in Table 1. There were no statistically significant differences in the parity distribution, mean gestation and mean height of the women. The mean infant birthweight was significantly greater (P=0·007) in the group who were delivered by CS for failure to progress in labour. The older women appear to be more likely to have a CS despite adequate augmentation. But analysis in maternal age subgroups revealed that only women aged >35 years were more likely to be delivered by CS (Fisher's test P=0·038). The mean length of labour and mean cervical dilatation before augmentation were similar. The mean length of labour after augmentation was longer (P=0·007) and the mean maximum dose of oxytocin was higher (P=0·002) in those women who were delivered by CS.

The pre-augmentation values for mean frequency and amplitude of contractions and mean uterine activity did not differ significantly between the CS and vaginal delivery groups (Table 2) and neither did the post-augmentation values. The increase in mean cervical dilatation was 1·7 cm over a mean augmentation period of 5·5 h in those patients who had a CS. In contrast the value was 5·8 cm in 3·8 h in those who were delivered vaginally. There was no scar rupture in the study population.

Discussion

The women in this study who had slow progress of labour had lower mean frequency, amplitude and UAI compared with the women reported previously (Arulkumaran 1989) who had a CS scar

Table 1. Obstetric and labour characteristics according to mode of delivery

Characteristic	Caesarean section (n=14)	Normal vaginal delivery (n=49)	P value
Age (years)	31·1 (4·0)	28·9 (3·4)	0·037
Height (cm)	153·7 (5·5)	154·7 (5·1)	NS
Birthweight (g)	3598 (383)	3230 (444)	0·007
Gestational age (weeks)	39·9 (0·9)	39·6 (0·2)	NS
Cervical dilatation (cm)			
At time of augmentation	4·0 (0·8)	4 2 (1·1)	NS
At time of delivery	5 7 (2·2)	10·0	0·000
Length of labour (h)			
Before augmentation	4·8 (2 3)	4·1 (1·6)	NS
After augmentation	5·5 (1·8)	3·8 (2 0)	0·007
Mean maximum dose of oxytocin (mU/min)	10·5 (2·0)	7·8 (2·9)	0·002

Results are mean (SD) values

NS, Not significant.

Table 2. Characteristics of uterine activity according to mode of delivery

	Caesarean section (n=14)	Normal vaginal delivery (n=49)
Frequency of uterine contractions/10 min		
Pre-augmentation	2·4 (0·86)	2·5 (0·71)
Post-augmentation	4·1 (0·75)	4·1 (0·6)
Amplitude (mmHg)		
Pre-augmentation	30·3 (6 7)	28·0 (7·4)
Post-augmentation	40·9 (9·9)	43·7 (10·5)
Uterine activity integral (kPas/15 min)		
Pre-augmentation	890 (247)	743 (239)
Post-augmentation	1655 (415)	1512 (363)

Results are mean values (SD).

but had spontaneous labour with normal progress. There was no clinical evidence of cephalopelvic disproportion, and because the reason for failure to progress was thought to be poor uterine activity, labour was augmented. The post-augmentation mean frequency (4 in 10 min) and amplitude (41–44 mmHg) were similar in the vaginal delivery and CS groups suggesting that an adequate uterine activity was achieved. Presumably, those with heavier babies had cephalopelvic disproportion and failed to progress despite adequate uterine activity for a sufficient length of time. Management of patients with previous CS and dysfunctional labour in this manner appears to be rational.

When uterine activity was calculated in UAI units, means of 1512 kPas/15 min in the vaginal delivery group and 1655 kPas/15 min in the CS group were recorded (Table 2). That is 15 and 25% higher, respectively, than the highest median uterine activity (1320 kPas/15 min) seen in women with a CS scar in spontaneous labour with normal progress (Arulkumaran *et al.* 1989). When labour is augmented in routine clinical practice the oxytocin infusion rate is titrated to achieve a mean frequency of 4 in 10 min. In our study this resulted in values of 167 Montevideo units (MU) (mean amplitude × number of contractions in 10 min) in the vaginal delivery group, and 179 MU in the CS group. When facilities for calculating the UAI are not available, computing uterine activity in Montevideo units may be used to assess whether adequate and not excessive uterine activity is produced as the result of augmentation because it is reasonable to believe that a higher uterine activity may increase the stress on the uterine scar. In addition, the duration of augmentation should be considered. If the progress of labour is poor in the presence of adequate uterine activity, prolongation of labour will increase the cumulative uterine activity with a probable increased risk of scar dehiscence.

In our study all the CS were for the indication of failure to progress in labour due to cephalopelvic disproportion. In these patients, the cervix dilated 1·7 cm over 5·5 h (0·3 cm/h) compared with 5·8 cm in 3·8 h (1·5 cm/h) in those who were delivered vaginally. Silver & Gibbs (1987) also found significant differences in cervical dilatation rate subsequent to the use of oxytocin in patients who were delivered vaginally (1·82 cm/h) compared with those who were delivered abdominally (0·18 cm/h). The cervical dilatation rate for the next few hours after oxytocin augmentation appears to be an important factor in predicting mode of delivery.

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Pregnancy following simple repair of the ruptured gravid uterus

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Summary. Eighteen pregnancies, occurring in 15 patients in whom a simple repair of a ruptured gravid uterus had been performed previously, are reviewed. Seventeen of these had a successful outcome. There was no case of recurrent rupture.

In cases of rupture of the gravid uterus, total abdominal hysterectomy is usually recommended as the treatment of choice (Bak & Hayden 1955; Feeney & Barry 1956; Ferguson & Reid 1958; Zeller *et al.* 1966; Eden *et al.* 1986). This view is based largely on isolated poorly documented reports of recurrent rupture during subsequent pregnancy in women who had had a simple repair of a ruptured uterus (Farrell 1967; Weingold *et al.* 1966).

Since Aguero & Kizer (1968) advocated simple repair without tubal ligation as a treatment option, little work has been published to assess their opinion. The present report shows that there is a place for conservative management in selected cases and one may expect a successful outcome of subsequent pregnancies if carefully managed.

Subjects and methods

Between January 1966 and December 1986 there were 67 cases of rupture of the gravid uterus in the Rotunda Hospital. Thirty-nine of these were classified complete and 28 incomplete. The diagnosis of complete rupture was only made when the full thickness of the uterine wall and overlying pelvic peritoneum were involved. Overall, 34 of these ruptures were considered suitable for repair, of which 12 were complete and 22 incomplete. All of these occurred in a previously scarred uterus.

We have traced 18 pregnancies in 15 patients in whom a simple repair was performed. Eight patients had a partial rupture involving the lower segment, while seven had a previous complete rupture. Five of these involved the lower uterine segment and two the upper uterine segment, one a previous classical scar and the other a small fundal rupture.

All but one of these repairs were performed using chromic catgut. In the remaining repair Dexon was used. The edges of the ruptured scar were freshened before repair in three cases; in the others simple reapproximation of the edges was made.

Seventeen of the pregnancies had a successful outcome; 16 of these were delivered by elective lower-segment caesarean section between 37 and 40 weeks gestation. The remaining patient, in whom repair of a previously ruptured classical scar had been performed, was delivered at 35 weeks gestation by lower-segment incision.

The one unsuccessful outcome occurred in a twin pregnancy, both fetuses were diagnosed as intrauterine deaths at 28 weeks. Spontaneous vaginal delivery of two macerated infants weighing 320 g each occurred 3 weeks later.

There was no significant maternal morbidity. The patients were not admitted to hospital for rest before delivery unless there was some specific indication such as hypertension or control of diabetes. No patient in this series was allowed to labour.

Discussion

In cases of rupture of a previous uterine scar, the defect can usually be sutured quite easily. In

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general, separation of a previous scar is relatively avascular and bleeds much less than a traumatic rupture, therefore the patient's general condition will be better. It is unclear if one should freshen the edges of the scar, as favoured by Pedowitz & Perell (1958) or simply reapproximate them (Groen 1974). From this series it would appear to make little difference, and as simple reapproximation is much easier it seems a reasonable choice. It may also be possible to perform a simple repair in many cases of rupture of the intact uterus, especially those that do not extend into the broad ligament or the vagina.

One of the main objections to simple repair without tubal ligation is the possibility of a recurrent rupture during a subsequent pregnancy. However, it is very difficult to assess this risk as few previous reports detail the outcome of these subsequent pregnancies. Weingold *et al.* (1966) state that two patients of seven in whom a repair was performed presented with a second rupture, but they give no details regarding these cases. One does not know if the rupture occurred in the patient's next pregnancy, or at what gestation, or under what circumstances it occurred. Farrell (1967), in a series of 13 patients in whom a repair was performed, states that two patients presented with recurrent rupture. Again, no details are given regarding the circumstances of these cases. Neither of these two reports, or those of Cavanagh *et al.* (1965) or Sall *et al.* (1967), give details of subsequent successful pregnancies which might put these cases of recurrent rupture in context.

Aguero & Kizer (1968) reviewed 66 subsequent pregnancies in 62 patients in whom a simple repair was performed. Fifteen of these had spontaneous vaginal deliveries. There were eight forceps deliveries, and 43 were delivered by caesarean section. There were four cases of recurrent rupture. All occurred in patients in whom vaginal delivery was allowed to take place.

The only other comprehensive report is that by Sheth (1968) who looked at 21 subsequent pregnancies in 13 patients. Seventeen of these pregnancies followed rupture of a lower-segment scar. Only one gave way. However, of the four pregnancies in the two patients in whom a classical scar was repaired, only one was successful. One patient suffered three successive ruptures before a hysterectomy was performed. It is noteworthy that none of these patients was delivered before 36 weeks gestation.

Sheth (1968) advocates that patients with a previously ruptured classical scar should be hospitalized from 28 weeks gestation and be delivered by caesarean section at 35 weeks, while those with a previously ruptured lower-segment scar should be hospitalized from 36 weeks and be delivered at 38 weeks gestation.

None of the patients in our series was hospitalized before delivery, unless there was a specific indication. However, it is probably prudent, especially in a case involving a previous ruptured classical scar, to advise in-patient monitoring.

Delivery should be by lower-segment caesarean section. The improvement in neonatal care makes the timing of this easier. Patients with previous ruptured classical scars should be delivered by 35 weeks, and those with previous lower-segment ruptures by 37 weeks gestation.

Undoubtedly, careful consideration should be given to performing a simple repair without tubal ligation in cases of rupture of a lower-segment scar especially in young patients, and in those whose family is not complete. While pregnancy in a patient with a previously ruptured classical scar is more hazardous, a successful outcome can be achieved, especially with planned early delivery.

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Amniotomy-induced labour is not mediated by endogenous oxytocin

S. THORNTON, J. M. DAVISON, P. H. BAYLIS

Summary. A technique for complete oxytocinase inhibition has been combined with a rapid serial sampling strategy to determine the plasma oxytocin concentration in eight women undergoing amniotomy for the induction of labour at term and in eight control women. Amniotomy was not associated with an increase in plasma oxytocin concentration. Furthermore, the concentrations were not increased for 20 min following the procedure. Labour was not established in any patient by the end of the 30-min study period.

Vaginal distension results in the release of oxytocin from the posterior pituitary via a neuroendocrine reflex (Ferguson 1941). The reflex has been described in the non-pregnant and lactating ewe (Debackere *et al.* 1961; Roberts & Share 1968), but may not occur during pregnancy (Roberts & Share 1968) due to a suppressive effect of maternal steroids (Roberts & Share 1969, 1970). Nevertheless, distension of the birth canal is believed to increase oxytocin release during delivery (Dyer 1988) and the Ferguson reflex may be responsible for the onset of human labour following amniotomy (Chard & Gibbens 1983).

There is good clinical evidence that amniotomy can initiate labour at term. The response may be mediated by systemic oxytocin (Llewellyn-Jones 1982), but clinical studies have produced conflicting results. The increase in plasma oxytocin reported by some workers (Vasicka *et al.* 1978; Chard & Gibbens 1983) has not been confirmed by others (Sellers *et al.* 1980; Nagata *et al.* 1983; De Geest *et al.* 1985).

The contradictory results can be explained, in part, by three major pitfalls specific to the measurement of oxytocin in human pregnancy. First, oxytocin may be released in a pulsatile manner (Chard *et al.* 1970; Vasicka *et al.* 1978); single samples may produce misleading results, and rapid serial sampling is mandatory if changes in plasma oxytocin concentration are to be accurately documented. Second, circulating oxytocin concentrations appear to be extremely low; the oxytocin antibody used in many of the early radioimmunoassays lacked the affinity required for the measurement of low hormone concentrations. Third, oxytocinase, a circulating placental enzyme produced by the human placenta, rapidly degrades oxytocin *in vitro* (Amico *et al.* 1984) and possibly *in vivo* (Thornton *et al.* 1988*a*). Failure to inhibit adequately the activity of this enzyme will lead to degradation of oxytocin in pregnancy blood samples. Furthermore, if the enzyme is not completely removed or destroyed by an extraction process, damage to the radiolabelled oxytocin used in the radioimmunoassay may lead to spuriously high values (Chard 1973).

To overcome these problems, we have combined a rapid serial sampling strategy (Thornton *et al.* 1987), adequate oxytocinase inhibition (Burd *et al.* 1987) and immediate sample extrac-

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Table 1. Characteristics of women in the two groups

	Amniotomy (n=8)	Control (n=8)
Age (years)	29·6 (6·5)	31·8 (7·1)
Parity (range)	0–1	0–3
Weight (kg)	81·8 (12·4)	73·4 (8·8)
Admission–delivery interval (h)	11·6 (5·9)	12·6 (9·6)
Method of delivery		
Normal vaginal	3	3
Forceps	2	2
Caesarean section	3	3

Results are mean (SD) values where appropriate.

tion with a sensitive and specific solid-phase radioimmunoassay to determine plasma oxytocin concentrations before, during and after amniotomy for the induction of labour at term.

Patients and methods

Sixteen patients (age range 18–42 years), admitted for induction of labour for obstetric indications, were recruited to the study and allocated randomly using sealed envelopes to one of the two management regimens. Eight patients underwent amniotomy 10 min after the start of the study and eight (control) were induced shortly after the end of the study period.

A 19-gauge indwelling intravenous cannula was inserted into a forearm vein 10 min before the start of sampling. Venous blood (4 ml) was drawn at 60-s intervals for 30 min. Following collection of sample 10, all patients were placed in the lithotomy position. Amniotomy (consisting of vaginal examination, digital dilatation of the cervix and artificial rupture of the membranes) was started before the collection of sample 11 in the eight patients assigned to undergo the procedure. The mean time taken for amniotomy was 4·1 min (range 2–7 min). The eight control patients (sham amniotomy) were placed in the lithotomy position for 5 min, but amniotomy and vaginal examination were deferred until the end of the 30-min study.

Each blood sample was taken into a chilled syringe containing 40 µl of the oxytocinase inhibitors 1, 10 phenanthrolene (125 mmol/l) and EDTA (1 mol/l), then immediately transferred to a chilled lithium heparin tube (Burd *et al.* 1987). Blood samples were centrifuged immediately at 2000 *g* for 15 min at 4°C and the plasma removed. Plasma samples were stored on ice before extraction within 1 h. Plasma aliquots (2 ml) were extracted by a Florisil/acetone technique (Beardwell 1971; Rooke & Baylis 1982; Burd *et al.* 1987) and stored at −20°C before solid-phase radioimmunoassay within 4 weeks. All samples from a single patient were assayed in triplicate in the same assay (detection limit 1·4 pmol/l, inter-assay coefficient of variation 9%, inter-assay coefficient of variation 14·8% at 10 pmol/l). Details of the assay and its characteristics have been published elsewhere (Burd *et al.* 1985, 1987). All patients gave informed consent to the study. Ethics committee approval was granted by Newcastle Health Authority.

Statistical analysis

Undetectable results (plasma oxytocin <1·4 pmol/l) were assigned the value of 1·4 pmol/l. The assigned value is the upper limit of that present since the true concentration is between 0 and 1·4 pmol/l. Consequently the calculated mean may be slightly higher than the true mean and is referred to as the 'upper limit of the mean'. Significance testing is inappropriate. For comparison with previous studies 1 pmol/l can be taken as 2 µ-units/ml oxytocin.

Results

The characteristics of both groups of patients are shown in Table 1. Many samples (74%) contained undetectable concentrations of oxytocin. The profile from a single patient in each group (in whom most samples contained more than 1·4 pmol/l) is shown in Fig.1. The results can be expressed as the upper limit of the mean before, during and after the procedure. The upper limit of the mean for each patient is shown in Table 2.

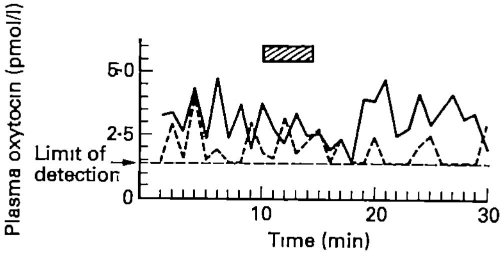

Fig. 1. Plasma oxytocin concentrations in (—) one woman who underwent amniotomy and (----) one woman who did not undergo amniotomy. ▨ indicates time of amniotomy or 'sham' amniotomy.

Table 2. Upper limit of the mean plasma oxytocin concentration (pmol/l) for each patient before, during and after amniotomy or sham amniotomy Concentrations below the detection limit are taken as 1·4 pmol/l

	Amniotomy			Control		
Patient	10-min basal	ARM	Post-ARM	10-min basal	Sham ARM	Post-sham ARM
1	4·8	4·9	4·5	1·4	1·4	1·4
2	1·6	1·4	1·4	1·4	1·4	1·4
3	3·3	2·8	3·1	1·4	1·4	1·4
4	1·5	1·5	1·8	1·4	1·4	1·4
5	1·4	1·6	1·7	2·1	1·4	1·5
6	1·4	1·4	1·4	1·6	2·2	1·8
7	1·4	1·4	1·4	1·4	1·9	1·4
8	1·4	1·5	1·6	1·5	1·4	2·4

ARM, Artificial rupture of the membranes

The upper limits were similar during and for 20 min after the procedure. Furthermore, the mean concentrations in the two groups were similar and the frequency of positive concentrations did not increase after amniotomy. Labour was not established in any patient by the end of the 30-min study period.

Discussion

Amniotomy was not associated with a rise in circulating plasma oxytocin concentration which was not increased during or for 20 min after amniotomy. The hormone concentrations were similar in the control group of patients throughout the sampling time. Our data are contrary to those reported by Chard & Gibbens (1983) in a study which utilized different techniques for the inhibition of oxytocinase activity. Similarly, Vasicka *et al.* (1978) report an increase in plasma oxytocin following vaginal examination or rupture of the membranes but samples were assayed without prior removal of oxytocinase, and proteolytic degradation of tracer may have led to spuriously high results.

Our results are more in keeping with those of Sellers *et al.* (1980), Nagata *et al.* (1983) and De Geest *et al.* (1985). The absence of an increase in plasma oxytocin following the cervical and vaginal distension associated with amniotomy may imply that the Ferguson reflex is inoperative during human pregnancy. This is unlikely since the increase in plasma oxytocin during the human third stage of delivery occurs immediately after the time of maximum vaginal distension and the Ferguson reflex may be responsible (Thornton *et al.* 1988*b*). The reason why vaginal distension may result in increased oxytocin release after delivery but not during amniotomy is that the former provides a much greater stimulus. Indeed, a major degree of distension is required to elicit the Ferguson reflex in the goat (Flint *et al.* 1975).

Since the plasma concentration remains low, oxytocin is unlikely to mediate the onset of labour following amniotomy unless (i) an increase in oxytocin release occurs more than 20 min after the start of the procedure, (ii) extremely low concentrations of oxytocin (<1·4 pmol/l) are required to elicit uterine contractions, or (iii) there is a sudden increase in receptor concentration.

It is unlikely that an increase in hormone concentration occurs more than 20 min after the procedure since the Ferguson reflex is normally associated with the immediate release of oxytocin (Roberts & Share 1969). Furthermore, concentrations of oxytocin below 1·4 pmol/l probably do not initiate labour. Infusion of 8 m-units/min (13·7 pmol/min) of synthetic oxytocin at term resulted in a mean (SE) concentration of 4·9 (1·0) pmol/l which was often below that required for the induction of labour (Thornton *et al.* 1988*a*) The onset of labour could, however, be due to an increase in receptor concentration. Receptors mediate the response to oxytocin during pregnancy (Fuchs *et al.* 1984) and may increase during labour. It is possible that the onset of labour is associated with an increase in receptor number rather than a change in plasma oxytocin concentration.

A likely mediator of parturition following amniotomy is prostaglandin F. An immediate rise in concentration of the metabolite of prostaglandin F (PGFM) has been demonstrated following amniotomy (Sellers *et al.* 1980; Husslein *et al.* 1983) although the magnitude of the increase is not correlated with the subsequent progress of labour. Nevertheless, the concentration of PGFM 2 h after the procedure does seem to be related to the induction–delivery interval (Husslein *et al.* 1983).

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Growth hormone 24-h serum profiles during pregnancy—lack of pulsatility for the secretion of the placental variant

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Summary. Serum profiles of growth hormone (GH) were recorded for 24 h in women at different stages of normal pregnancy. Two monoclonal antibodies directed against different epitopes and unaffected by human placental lactogen were used in radioimmunoassays to distinguish the pituitary 22K-GH from the placental GH variant. The 'normal' episodic peak activity of GH in non-pregnant and first trimester pregnant women was dramatically changed into a continuous very stable secretion during late pregnancy. This change was first observed at 17 weeks gestation. It is concluded that during the second half of pregnancy, serum measurements of GH reflect a major contribution from a non-episodically secreted placental GH variant and a concomitant suppression of pituitary GH. This specific signal, i.e. a continuous GH secretion, may be an important regulator of maternal liver metabolism during pregnancy.

Growth hormone (GH) is a major metabolic regulatory hormone which stimulates protein synthesis and has profound effects on carbohydrates and lipid metabolism (Merimee 1979). In recent studies on the physiology of growth hormone in pregnant women (Frankenne *et al.* 1988), we have shown that maternal serum levels of the pituitary 22K hGH, encoded by the GH-N gene, are very low during the second half of pregnancy. Increasing concentrations of a placental GH variant, most probably encoded by the GH-V gene (Frankenne *et al* 1987), are recorded from mid-pregnancy until term. Placental GH has been partially characterized (Frankenne *et al.* 1988; Hennen *et al.* 1985*a*) and, importantly, has been shown to behave as a strong agonist to pituitary GH in the binding to hepatic GH receptors It can be readily distinguished from the pituitary 22K-hormone by its specific pattern of immunoreactivity towards anti-GH monoclonal antibodies (Hennen *et al.* 1985*b*).

In animals as well as normal men and non-pregnant women, GH is secreted in episodic bursts with low or undetectable levels between peaks (Zadik *et al.* 1985; Ho *et al.* 1987). In a previous report, using an assay not discriminative for pituitary and placental GH variants, we demonstrated a dramatic change in growth hormone secretion during late pregnancy (Eriksson *et al.* 1988*a*). The pulsatile pattern characteristic

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of the non-pregnant state was completely abolished and transformed into a continuous, stable secretion. The potential biological impact of such a non-pulsatile secretion is well known from animal experiments (Jansson *et al.* 1985). When episodic GH secretion is transformed into a continuous pattern, a variety of metabolic functions are affected. Significant changes as regards hepatic steroid metabolism, enzymatic activity, receptor and plasma protein synthesis have been demonstrated (Eden *et al.* 1987).

In the present study, 24-h secretory profiles of GH were established for individual women during different stages of normal pregnancy, and two monoclonal antibodies were used to distinguish between the pituitary and the placental GH variant (Hennen *et al.* 1985*b*)

Subjects and methods

The study included 11 pregnant and two non-pregnant women. Six women were in the third trimester (gestational week 34–40) of an apparently normal singleton pregnancy. Two women were at 10 and 16 weeks gestation. Three women were investigated before and after vaginal (weeks 10 and 12) and intra-amniotic (week 15) prostaglandin administration for legal abortion. In all women gestational age was confirmed by ultrasound. Two women in the follicular and luteal phase of an apparently normal menstrual cycle served as controls.

Sample collection

Women in late pregnancy were admitted to the hospital in the morning of the day of sampling whereas those in early pregnancy were already hospitalized before legal abortion. The study was approved by the local ethics committee and all women gave their informed consent to participate. Blood samples were obtained using the non-thrombogenic blood withdrawal system according to Kowarski *et al.* (1971). In some women an indwelling catheter kept patent by 0·9% saline infusion was necessary to allow repeated sampling.

Blood samples, approximately 5 ml each, were collected at 30-min intervals during a period of 24 h. In three pregnant women the study was interrupted after 10–14 h because of blood clotting. All blood samples were centrifuged free of formed elements and sera were stored at −20°C blind in duplicate. The activity and food intake of subjects was recorded but not in any way restricted. Walking and daily activities, including housework and moderate exercise, were encouraged and the subjects were allowed to retire after 22.00 hours. The period of sleep was recorded by observations of the investigators.

Radioimmunoassay

Two monoclonal antibodies raised against purified GH variants and coded 5B4 and K24 were used in two radioimmunoassays (RIA) as described previously (Gomez *et al.* 1984). The immunochemistry of the two monoclonal antibodies and the characteristics of the related assays have been reported previously (Frankenne *et al.* 1988; Hennen *et al.* 1985*a*).

Briefly, the affinity constants (Ka) of the binding reaction with the 22K hGH were 5×10^9 M^{-1} and $1{\cdot}02 \times 10^{11}$ M^{-1} for the two antibodies K24 and 5B4 respectively. The monoclonal antibody 5B4 was found to be directed towards the N-terminal epitope and to recognize all known pituitary as well as placental GH variants; K24 reacted with a more internally located epitope and recognized the 22K pituitary GH but not the placental variant. Placental GH could therefore be distinguished from the pituitary 22K GH by its lack of reactivity with K24. Human placental lactogen (hPL) was unable to compete with ^{125}I-labelled 22K GH for the binding to both monoclonal antibodies even at a dose of 10 μg/ml.

All analyses on an individual subject were performed in a single assay. All GH standards were calibrated against IRP 66/217 from WHO and expressed as mU/l. Sensitivities of the assays were 2 mU/l (K24 RIA) and 0·5 mU/l (5B4 RIA). The intra- and interassay variation for the K24 RIA was 4·6 and 11·3% and for the 5B4 RIA 4·0 and 9·8%. The cross-reactivity with hPL and prolactin in both assays was less than 0·01%.

Results

The growth hormone 24-h profile values for one non-pregnant woman during the luteal phase of the menstrual cycle are shown in Fig. 1. The woman investigated during the follicular phase displayed a quite similar pattern. The high correlation between the two assays was apparent and a marked episodic peak activity was recorded. K24 RIA baseline levels were low and mostly around the detection limit (2 mU/l) while 5B4

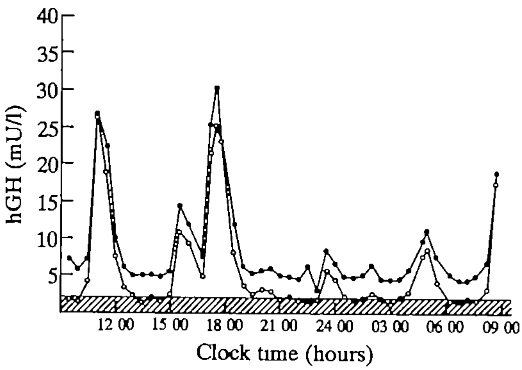

Fig. 1. Secretory profile of growth hormone in serum (mU/l) assessed by two different assays in one woman during the luteal phase of the menstrual cycle. The detection limit of the K24 RIA is indicated by hatched bars ●, 5B4 RIA; ○, K24 RIA

RIA baseline values were higher, ranging 5–7 mU/l.

Figure 2 illustrates GH serum concentrations in one woman investigated at 11 weeks gestation. Again frequent episodic peaks up to 25–35 mU/l were observed. Also in the two women investigated at 10 and 12 weeks gestation before and after receiving vaginal prostaglandin, the same close parallelism between the assays and frequent high peaks, possibly enhanced during uterine contractions were recorded. As compared with the non-pregnant women both RIAs measured a slight increase in basal levels.

The obvious episodic peak activity of GH in the non-pregnant and first trimester pregnant women could not be demonstrated during a normal pregnancy at 17 weeks. As shown in Fig. 3 immunoreactivities recorded with both assays indicated a more continuous hormone secretion. The same picture of a reduced pulsatile activity was found at 15 weeks gestation in one woman before and after intra-amniotic prostaglandin administration. 5B4 RIA values were around 5–8 mU/l whereas the K24 RIA values were clearly lower.

During late pregnancy all six women investigated showed the same pattern of GH secretion. Typical values from one woman are shown in Fig. 4. The difference between late pregnancy and the non-pregnant state was apparent. The immunoreactivities recorded here were even more stable and continuous than those recorded at 17 weeks (Fig. 3). The 5B4 RIA levels ranged from 19 to 24 mU/l and K24 RIA values were very low, mostly below the limit of detection (2 mU/l).

Discussion

We reported previously that the episodic, pulsatile 24-h secretion of maternal GH is markedly changed during late pregnancy when compared with the non-pregnant state (Eriksson *et al.* 1988*a*). This change could reflect differences in the mode of secretion between distinct GH variants. A placental GH variant has been found to predominate in maternal serum after the first trimester (Frankenne *et al.* 1988; Hennen *et al.* 1985 *a,b*). Specific reactivities with the 5B4 and K24 anti-GH monoclonal antibodies enabled us to distinguish between pituitary GH (reacting with both antibodies) and placental GH (reacting with the 5B4 antibody only) in serum samples from pregnant women obtained during 24 h.

At the end of the first trimester (10–12 weeks gestation), the 24-h evolution of GH levels, as well as the GH immunoreactivity pattern, were similar to those in non-pregnant women. Although basal levels were slightly elevated the frequent pulsatile activity, characteristic for these women, was readily detected. All secretory peaks were simultaneously recorded by both methods. Hence, only pituitary GH was evidenced. The slight disparity between absolute values was of the same magnitude as observed previously in non-pregnant subjects in a comparison between different assays using monoclonal antibodies (Levin *et al.* 1987).

In the beginning of the second trimester (15 and 17 weeks gestation) a dramatic change was observed. Significant amounts of placental GH were present in maternal serum, as shown by

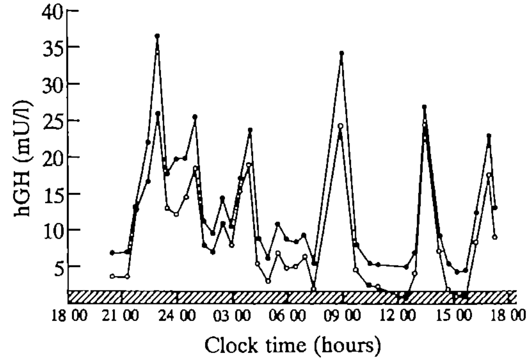

Fig. 2. Secretory profile of growth hormone in serum (mU/l) assessed by two different assays in one woman at 11 weeks gestation. The detection limit of the K24 RIA is indicated by hatched bars ●, 5B4 RIA, ○ K24 RIA.

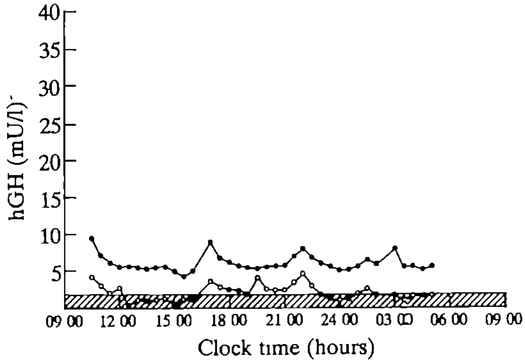

Fig. 3. Secretory profile of growth hormone in serum (mU/l) assessed by two different assays in one woman at 17 weeks gestation. The detection limit of the K24 RIA is indicated by hatched bars. ●, 5B4 RIA, ○, K24 RIA.

much higher levels recorded for the 5B4 immunoreactivity than for the K24 assay. Furthermore, the 24-h secretory profile was much more stable than in the first trimester. The radioimmunoassays were not affected by hPL and the recorded profiles might be interpreted to indicate a major contribution from a non-episodically secreted placental GH variant and a concomitant suppression of pituitary GH.

Finally, during late pregnancy, the extinction of 'normal' growth hormone pulsatility was apparent in all six women (Fig. 4). The 5B4 assay read serum concentrations ranging from 25 to 30 mU/l whereas the K24 RIA values were all below the limit of detection (2 mU/l) indicating a suppression of pituitary GH secretion. Thus, it seems reasonable to conclude that high levels of only placental GH were assayed in maternal serum. Interactions between GH and circulating binding proteins might influence the absolute concentrations recorded during late gestation A specific high-affinity low-capacity binding protein has been demonstrated in normal human plasma (Bauman et al 1986). Increasing concentrations during late pregnancy of such a binding protein, which might interfere with the internal epitope of the hormone, might possibly to some extent reduce the values obtained by the K24 RIA. This seems unlikely since serum GH immunoreactivity is mainly associated with 20 000 to 30 000 molecular weight proteins, as evidenced by gel filtration in late pregnancy sera (F. Frankenne, unpublished results). It should also be recalled that protease activity during late pregnancy is high. Protease degradation might to some extent change the proportion of different circulating forms of GH and interfere with the binding to different antibodies (Wallis et al. 1982). However, this should not change the main conclusion that during late pregnancy serum measurements of GH reflect a major contribution from the placental variant.

The results reported here clearly suggest that, unlike pituitary GH, the placental GH variant is essentially secreted in a continuous fashion. The biological significance of this specific signal, i.e. a stable continuous GH secretion, is well known in animals and has dramatic effects on a variety of metabolic functions including steroid metabolism, enzymatic activities, receptor and plasma protein synthesis (Jansson et al. 1985; Eden et al. 1987). The mammalian liver is a target organ for GH. The presence of GH was found to be necessary for steroid-induced protein synthesis in liver slices (Griffin & Miller 1974) and to stimulate creatine kinase activity in rat liver and other tissues (Golander et al. 1986). Furthermore, continuous exposure to GH seems to be required for up-regulation of liver GH receptors (Maiter et al. 1988). Recent experiments on murine analogues to human pregnancy-associated proteins have demonstrated a rapid and stimulatory effect of continuous, but not of intermittent, GH administration (Frohlander et al. 1987; Eriksson et al 1988b).

It is of particular interest in this context that the chorionic GH-like antigen probably expressed in the B54 RIA has been reported to have a particularly high affinity for liver GH receptors (Hennen et al. 1985b). Further studies on the interaction

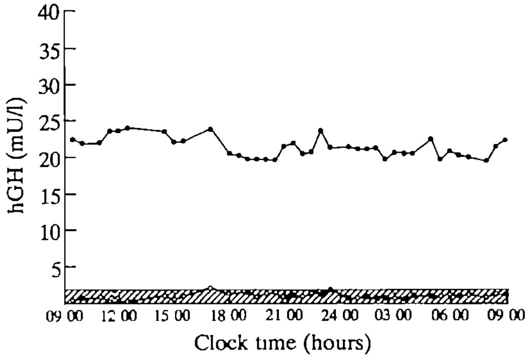

Fig. 4. Secretory profile of growth hormone in serum (mU/l) assessed by two different assays in one woman at 34 weeks gestation. The detection limit of the K24 RIA is indicated by hatched bars ●, 5B4 RIA; ○, K24 RIA

between GH variants and maternal liver function during pregnancy may increase our understanding of the physiological adjustment to gestation and also have clinical implications.

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Transvaginal ultrasonic assessment of endometrial growth in spontaneous and hyperstimulated menstrual cycles

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Summary. Endometrial thickness and reflectivity were assessed by transvaginal ultrasound in both spontaneous and hyperstimulated menstrual cycles. Two groups of women with ovulatory cycles were examined; women in group 1 had unexplained infertility and women in group 2 were having artificial insemination by donor because of reduced spermatogenesis; a third group (group 3) comprised women with tubal infertility undergoing hyperstimulation for in-vitro fertilization. There was no difference in endometrial thickness or reflectivity between the three groups. A basic pattern of endometrial appearance common to all cycles was found, consisting of hypoechoic, isoechoic and hyperechoic images, occurring in the early follicular, late follicular and luteal phases, respectively. In all three groups a positive correlation was found between proliferative phase plasma oestradiol concentration and endometrial thickness. Group 1 $r = 0{\cdot}403$, $P<0{\cdot}01$; group 2 $r = 0{\cdot}439$, $P<0{\cdot}01$; and group 3 $r = 0{\cdot}617$, $P<0{\cdot}01$. There was a progressive increase in endometrial growth throughout the normal cycle until a plateau was reached 5 days after the LH surge. This pattern was also seen without acceleration of the process in hyperstimulated cycles, despite supranormal levels of oestrogen. Assessment of endometrial thickness is not a useful variable in monitoring hyperstimulated cycles. No aberrations of endometrial growth or pattern were observed in the women with unexplained infertility.

Ultrasonography of the endometrium provides a non-invasive method of monitoring end-organ response to circulating steroids. Several studies have described changes in endometrial reflectivity patterns during the normal menstrual cycle (Hackelöer 1984; Sakamoto & Nakano 1982; Smith *et al.* 1984; Fleischer *et al.* 1984, 1986*c*). Other studies have compared endometrial growth (Imoedemhe *et al.* 1987) and volume (Giorlandino *et al.* 1987) in spontaneous and induced cycles. Some have suggested that ultrasonic measurement of endometrial development facilitates improved monitoring in in-vitro fertilization (IVF) cycles (Smith *et al.* 1984; Glissant *et al.* 1985), particularly as sex steroid levels may be of limited value in predicting endometrial development (Cohen *et al.* 1984; Garcia *et al.* 1984).

Differences in endometrial reflectivity and

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growth patterns in conception and non-conception cycles have been reported (Brandt *et al.* 1985), although not confirmed (Fleischer *et al.* 1986*b*). Rabinowitz *et al.* (1986) have suggested that a minimal endometrial thickness in the luteal phase is a necessary prerequisite for implantation.

The above studies were all performed with transabdominal ultrasonography. The recent introduction of vaginal ultrasound probes has permitted the use of higher frequency ultrasound at greater proximity to the uterus to produce superior resolution (Drugan *et al.* 1988; Schwimer & Lebovic 1984). This technique is both accurate (Yee *et al.* 1987) and well tolerated, avoiding the discomfort associated with the transabdominal full bladder technique.

The aim of the study was to examine endometrial development in patients with unexplained infertility and patients undergoing ovarian hyperstimulation for IVF in addition to reassessing ultrasound classifications of endometrial development using the transvaginal route.

Subjects and methods

Three groups of women were recruited and had the research explained to them before they gave written consent to participation. Studies were approved by the institutional ethics committee.

Group 1 (23 cycles)

Ten women with unexplained infertility identified by established criteria (Templeton & Penney 1982) underwent alternative cycles of intraperitoneal insemination and transvaginal oocyte recovery, in spontaneous cycles. No luteal support was administered. Transvaginal ultrasound measurements were made in 23 cycles; four patients underwent three cycles and one patient a single cycle.

Group 2 (10 cycles)

Ten women whose partners had reduced or absent spermatogenesis were recruited from among those receiving donor insemination. Each woman had a laparoscopically confirmed normal pelvis and tubal patency. Progesterone levels were confirmed with ovulation, i.e. >30 nmol/l in the mid-luteal phase of at least two cycles. These patients were regarded as normal controls.

Group 3 (14 cycles)

This group comprised nine women with bilateral tubal occlusion and no previous livebirths, who were having multiple folliculogenesis stimulated for IVF. Superovulation was induced with clomiphene citrate, 150 mg daily, day 2–6, and urofollitrophin (Metrodin, Serono), 75 iu intramuscularly on days 4 and 5 and then 150 iu daily. Follicular development was monitored by vaginal ultrasonography, and 5000 iu of hCG were administered when the mean follicular diameter of the leading follicle was >18 mm. Oocytes were recovered transvaginally 34 h later under premedication (pethidine 100 mg, diazepam 10 mg) and local anaesthesia. Luteal phase support was not administered.

Vaginal ultrasonography

Ultrasound used a Diasonics DRF 200, utilizing a Diasonics 7·5 mHz IVE probe (Diasonics Sonotron, Bedford) with a frame rate of 15 /s and a 95° field of view. The focal zone was 1·5–6·5 cm, and depth of field 7 cm. Measurements were made by one of two operators. The endometrium was displayed in a standard plane by aligning the uterus along the central longitudinal axis, avoiding a tangential view. The endometrial thickness was measured from the echogenic interface of the junction of endometrium and myometrium. This measurement represents two layers of endometrium (Fleischer *et al* 1986*a*). The hypoechogenic halo was not included in the measurement, as this represents the inner layers of compact and vascular myometrium (Fleischer *et al.* 1986*c*). Vaginal ultrasonography was performed daily from day 8 in groups 1 and 2 and day 6 in group 3. In groups 1 and 2 the day of onset of the LH surge, as defined previously by Messinis *et al.* (1985), was denoted as LH−0. In group 3, this was taken as the day of hCG administration. All women were investigated by ultrasound daily until LH−0, then at LH+1, LH+5 and LH+10 days.

Biochemical studies

Venepuncture was performed daily at the same time as ultrasonography until LH−0 and then on alternate days. Serum LH was measured using

Table 1. Endometrial thickness measurements by transvaginal sonography by day of onset of LH surge or day of hCG administration in hyperstimulated cycles

Day of measurement		Double endometrial thickness (mm)				
	n	Group 1 (23 cycles)	*n*	Group 2 (10 cycles)	*n*	Group 3 (14 cycles)
LH−5	14	7·4 (0·8)	7	4·6 (0·4)	5	5·4 (1·2)
LH−4	17	7·9 (0·6)	8	5·5 (0·5)	8	5·7 (0·7)
LH−3	18	7·9 (0·6)	9	6·3 (0·4)	9	6·1 (0·8)
LH−2	18	9·6 (0·6)	10	7·0 (0·5)	10	6·6 (0·6)
LH−1	22	10·0 (0·5)	10	8·2 (0·5)	9	8·0 (1·0)
LH−0	19	9·5 (0·5)	9	7·7 (0·6)	11	8·7 (0·9)
LH+1	14	9·9 (0·6)	6	8·8 (0·7)	7	7·8 (0·8)
LH+5	21	12·0 (0·6)	8	9·2 (0·4)	7	8·7 (0·8)
LH+10	17	12·3 (0·9)	7	10·1 (0·6)	6	8·8 (1·6)

Results are mean (SEM) values, *n* =number of observations.
Group 1=unexplained infertility, group 2=normal controls, group 3=hyperstimulated cycles.

monoclonal antibodies in a immunoradiometric assay (IRMA) (Serono Diagnostics), and results expressed as miu/ml. The LH standard was calibrated against WHO First International Reference Preparation IRP 68/40(1). The lower limit of LH detection was 0·5 miu/ml, and the inter- and intra-assay variations were 7·8% and 6%, respectively. Serum oestradiol was measured in nmol/l using a Serono Diagnostic MAIA kit; results were expressed in nmol/l. The lower limit of detection was 60 pmol/l, and inter- and intra-assay variations were 6·3% and 3% respectively.

Statistical analysis

This was performed using one-way analysis of variance (ANOVA). Correlations were analysed with Pearson's correlation coefficient. Endocrine data were log normalized with the aid of a Minitab package (Statistics Department, Pennsylvania State University).

Results

Endometrial growth was similar in spontaneous and hyperstimulated cycles (Table 1). Endometrial thickness in groups 1 and 3 fell within the range of the control cycles shown in Fig. 1. In all cycles an increasing thickness was found during the follicular phase which plateaued in the luteal phase. In hyperstimulated cycles the endometrial thickness was within the normal range despite having significantly higher oestradiol levels than were found in spontaneous cycles (ANOVA) (Fig. 2). A significant increase in endometrial thickness from LH−5 to LH−0 occurred in all groups (group 1: $F_{5,102}$ = 3·31, *P*<0·01; group 2: $F_{5,47}$ = 7·29, *P*<0·01; group 3: $F_{5,46}$ = 2·35, *P*<0·05, by ANOVA).

There was a significant correlation in the follicular phase of both spontaneous and hyperstimulated cycles between oestradiol and endometrial thickness (group 1: *r* = 0·403, d.f. 119, *P*<0·01; group 2: *r* = 0·439, d.f. 57, *P*<0·01; and group 3: *r* = 0·617, d.f. 50, *P*<0·01).

Three distinct patterns of endometrial reflectivity were noted. These were seen consistently in all cycles (Fig. 3). In the early follicular phase there was a hypoechoic area around a prominent

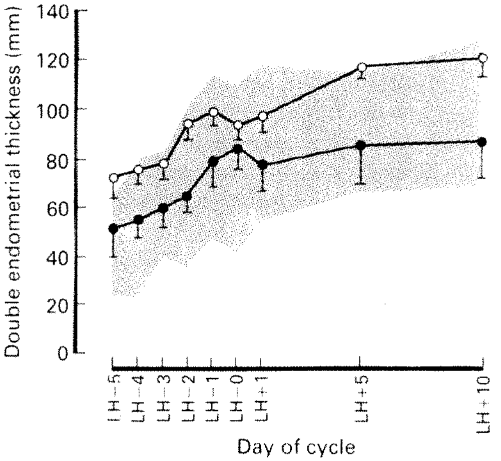

Fig. 1. Double endometrial thickness mean (SEM) in patients with unexplained infertility (○) and hyperstimulation cycles (●). Shaded area depicts 95% data intervals for control patients.

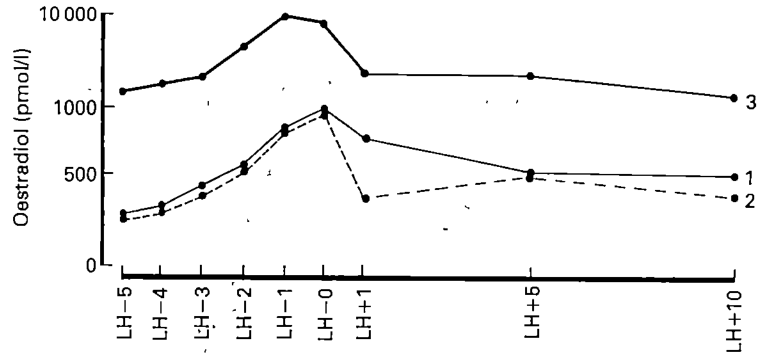

Fig. 2. Serum oestradiol mean in the three groups of patients plotted on a log scale related to day of onset of spontaneous LH surge or the day of administration of hCG in hyperstimulation cycles (LH–0). Group 1 = unexplained infertility, group 2 = normal controls, group 3 = hyperstimulated cycles

midline echo. By the late follicular phase reflectivity in the endometrium had increased to appear isoechoic with the myometrium, while in the mid-luteal phase the endometrium became hyperechoic, blurring the midline echo

Discussion

This study characterizes endometrial development in spontaneous and stimulated cycles using the superior transvaginal technique. Endometrial growth in unexplained infertility was comparable with controls while their qualitative echogenicity patterns were identical. During the study cycles the women with unexplained infertility had a normal sex steroid secretion pattern, and ovulatory follicle rupture occurred spontaneously.

Our values for endometrial thickness are in agreement with previous reports (Fleischer *et al* 1986*c*; Imoedemhe *et al.* 1987). A maximal endometrial response occurs in spontaneous cycles and is neither enlarged nor accelerated in stimulated cycles, despite significantly higher oestradiol levels.

Endometrial thickening, therefore, appears to be a function of duration of exposure to oestrogen rather than the absolute concentration. This may occur in pathological states, such as cystic glandular hyperplasia, where it is recognized that prolonged exposure to levels of oestrogen insufficient to cause positive feedback can nevertheless cause endometrial hypertrophy. This has been postulated as the reason for increased endometrial thickness in patients with polycystic ovarian syndrome (Adams *et al.* 1988). However, a further explanation for normal endometrial development in hyperstimulated cycles could be the anti-oestrogenic effect of the clomiphene on the endometrium, negating the effects of increased steroid levels. Imoedemhe *et al.* (1987) compared superovulation regimens with and without clomiphene and found that those containing clomiphene produced endometrium which was thinner although still within the range of controls.

In this study, endometrial thickness in spontaneous cycles correlated significantly with increased steroid levels as reported previously (Hackeloer 1984; Adams *et al.* 1988). However, Giorlandino *et al.* (1987) could only find a significant correlation between oestradiol and endometrial thickness in stimulated cycles

Cyclical patterns of endometrial reflectivity have been described previously (Hackeloer 1984; Smith *et al.* 1984), although some studies have not found these changes to be as consistent with the cycle phase (Sakamoto & Nakano 1982; Fleischer *et al.* 1984) as shown in our study. Furthermore, Smith *et al.* (1984) and Hackeloer (1984), with transabdominal ultrasonography, identified four and six types respectively of endometrial appearance during each cycle, whereas in this study, using vaginal ultrasonography with superior resolution, only three basic echo-patterns could be discerned. Such reflectivity patterns are supported by histological and morphological changes during the menstrual cycle (Fleischer *et al.* 1986*a*). The gradual increase in reflectivity from hypoechoic to hyperechoic during the cycle seems related to increasing tortuosity of endometrial glands, mucin storage and secretions, all of which alter

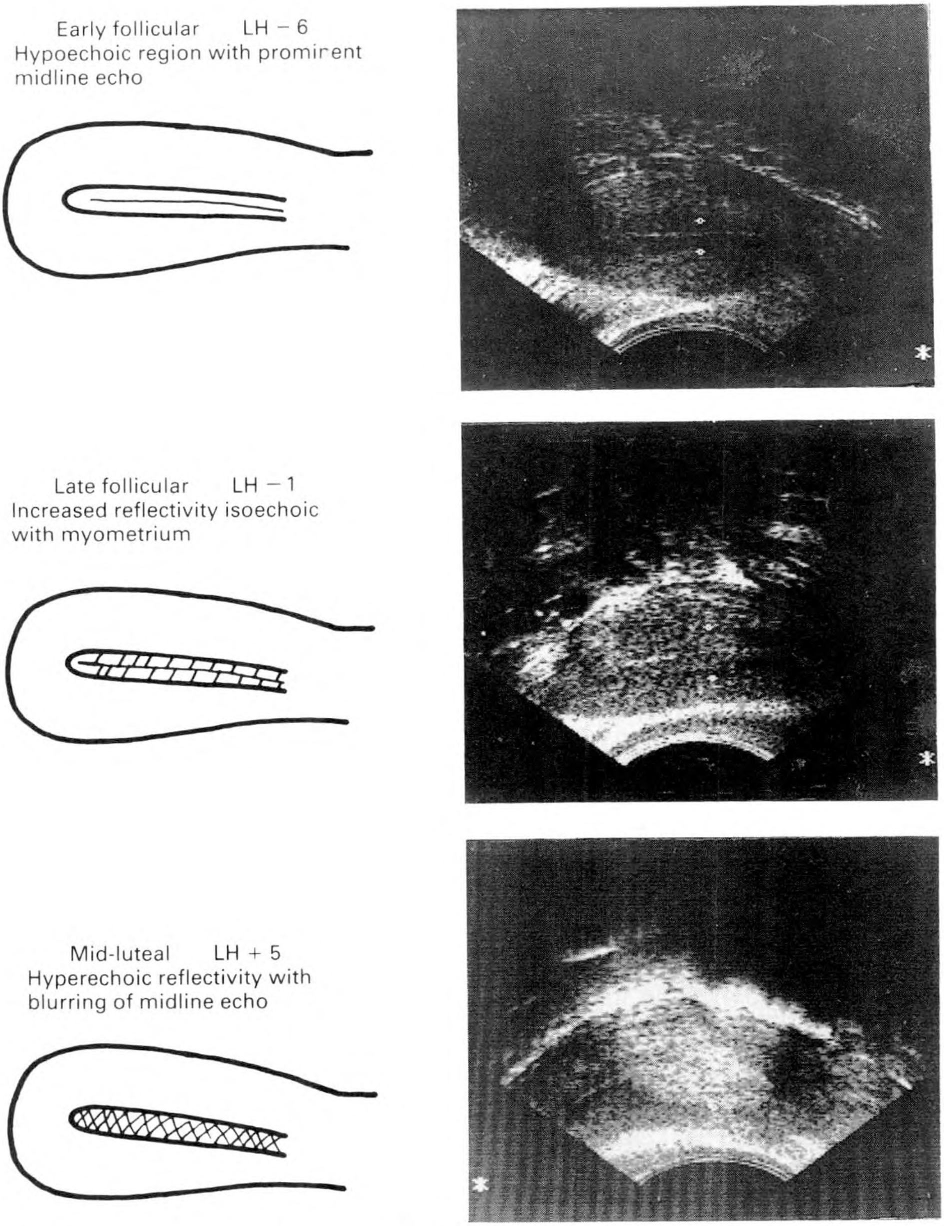
Early follicular LH − 6
Hypoechoic region with prominent midline echo
Late follicular LH − 1
Increased reflectivity isoechoic with myometrium
Mid-luteal LH + 5
Hyperechoic reflectivity with blurring of midline echo

Fig. 3. Endometrial reflectivity patterns during the menstrual cycle in the early follicular, late follicular and mid-luteal phases.

the reflectance of tissue. In view of the conflicting classification in the literature of qualitative endometrial development assessed by transabdominal scanning, we propose a simpler classification based on transvaginal sonography, consisting of hypoechoic, isoechoic and hyperechoic endometrial reflectivity.

It seems unlikely that endometrial reflectivity assessment will prove predictive of success in in-vitro fertilization cycles, as the basic changes in endometrial morphology outlined in this study are common to all cycles. Endometrial reflectivity patterns, however, may be used as another variable for the assessment of ovulation.

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The effect of intravascular transfusion for rhesus haemolytic disease on umbilical artery Doppler flow velocity waveforms

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Summary. To test the hypothesis that an increase in fetal blood viscosity is associated with an increase in resistance to flow, the effect on Doppler flow velocity waveforms of percutaneous umbilical blood sampling and intravascular transfusion was studied in 20 patients undergoing a total of 35 procedures. All but four of the 22 transfusions were associated with a decrease in resistance to flow, as shown by a reduction in the umbilical artery systolic/diastolic ratio, and this also occurred on 10 of the 13 occasions when blood sampling only was performed. These findings suggest that acute changes in blood viscosity following intravascular transfusion are not associated with an increase in resistance to flow as assessed by Doppler velocimetry. Umbilical blood sampling *per se* may be associated with a humorally mediated reduction in placental vascular resistance to flow.

Abnormal Doppler flow velocity waveforms from the umbilical artery appear to be early indicators of fetal compromise (Cameron *et al.* 1988), and the availability of Doppler velocimetry may improve obstetric decision-making (Trudinger *et al.* 1987).

Nevertheless, the underlying pathophysiology of abnormal waveforms remains uncertain. One mechanism may involve the obliteration of tertiary stem villus arterioles, which has been found in association with abnormal waveforms (Giles *et al.* 1985; McCowan *et al.* 1987), but the observed return of previously absent end-diastolic velocities in a severely compromised pregnancy (Hanretty *et al.* 1988) suggests that an obliterative process is not always present and that other factors may operate.

Viscosity has an important influence on blood flow and an association has been reported between high viscosity in cord blood at delivery and elevation of the systolic/diastolic ratio (Stuart *et al.* 1980) in the umbilical artery (Giles *et al.* 1986). However, the influence of blood viscosity *in utero* on Doppler waveforms remains uncertain. To study this, we have used as a model the severely 'rhesus-affected' fetus undergoing intravascular blood transfusion which raises the fetal haematocrit and thus also its blood viscosity.

Interpretation of the direct measurement of fetal blood viscosity is methodologically difficult (Jouppila *et al.* 1986) but, since a linear increase

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in haematocrit is associated with a logarithmic increase in viscosity (Lowe 1987) and its measurement is independent of shear rate, the haematocrit can be used as an indirect index of viscosity. We report a comparative study of the effect of percutaneous umbilical blood sampling and intravascular transfusion on umbilical artery waveforms.

Subjects and methods

Flow velocity waveforms were obtained from the umbilical artery in 20 patients who underwent a total of 35 percutaneous umbilical blood sampling procedures. This was performed in 16 to assess the severity of rhesus haemolytic disease, and on 22 occasions intravascular transfusion was indicated by the results obtained; on three occasions blood samples were obtained to provide a rapid fetal karyotype, and in one case to determine the fetal adenosine deaminase activity.

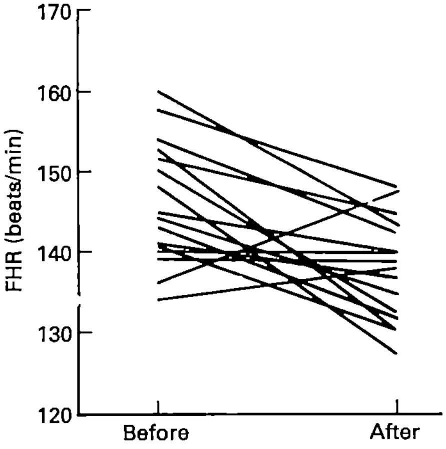

Fig. 1. Fetal heart rates (FHR) before and after transfusion.

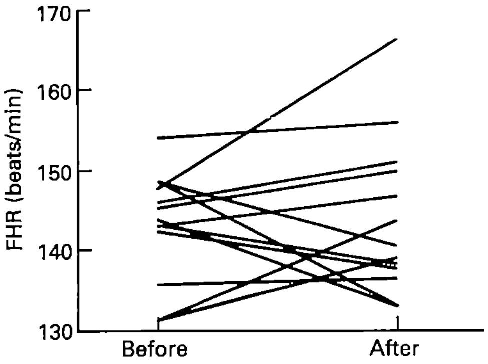

Fig. 2. Fetal heart rates (FHR) before and after blood sampling only

Premedication with lorazepam, papaveretum and fentazine was used in all but three procedures. Measurements were made after premedication and immediately before the procedure. Pretransfusion and, when possible, post-transfusion haematocrits were recorded. The systolic/diastolic ratio and fetal heart rate were measured from the umbilical artery flow velocity waveform before the procedure and 1 h after beginning sampling, using a continuous wave Doppler system (Doptek Ltd, Chichester). Patients were studied in the semirecumbent or left lateral position to avoid the risk of supine hypotension syndrome. For each measurement five consecutive representative waveforms were obtained during a period of fetal apnoea, and the mean of these values was then corrected for heart rate using the formula reported by Mires *et al.* (1987). Comparisons were made between pre- and post-procedure values by the Wilcoxon test. The values from the transfused fetuses were compared with those who had blood sampling without transfusion, using the Mann–Whitney test.

Results

The mean haematocrit before transfusion was 23·6 (SD 8·7)%, and the mean increase in haematocrit was 17·1 (SD 6·5)% ($n = 20$) following a mean infusion of 49·2 (SD 26) ml of packed cells. The mean increase in fetal haematocrit, when expressed as a percentage of pretransfusion haematocrit, was 103 (SD 87)%. There was a reduction in fetal heart rate after all but two transfusions (mean heart rate 144, SD 6·8 before, and 139, SD 8·8 at 1 h: $P<0{\cdot}03$) but no trend was observed in heart rate in the fetuses who had percutaneous umbilical blood sampling alone (mean heart rate 143, SD 6·7 before, and 144, SD 9·9 at 1 h) (Figs 1 and 2). This difference in response was significant ($P<0{\cdot}04$). Both sampled and transfused groups showed reductions in the systolic/diastolic ratio following the procedure (Figs 3 and 4) (corrected systolic/diastolic ratio 3·65, SD 1·27 before sampling and 3·08, SD 0·8 at 1 h, and 3·4, SD 1·0 before transfusion and 2·95, SD 0·8 at 1 h; $P<0{\cdot}03$ for both groups) and there was no significant difference in response between the two groups.

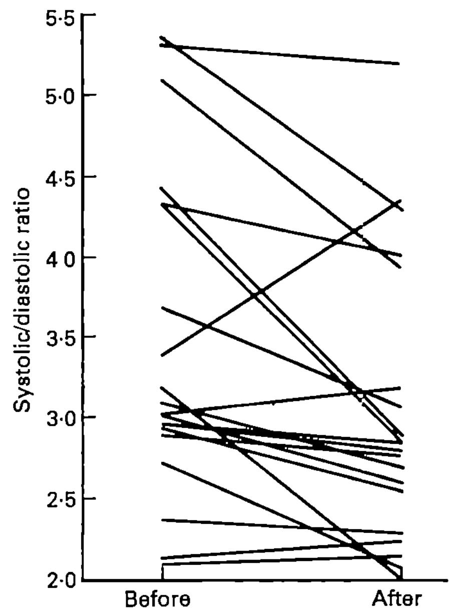

Fig. 3. Systolic/diastolic ratio before and after transfusion.

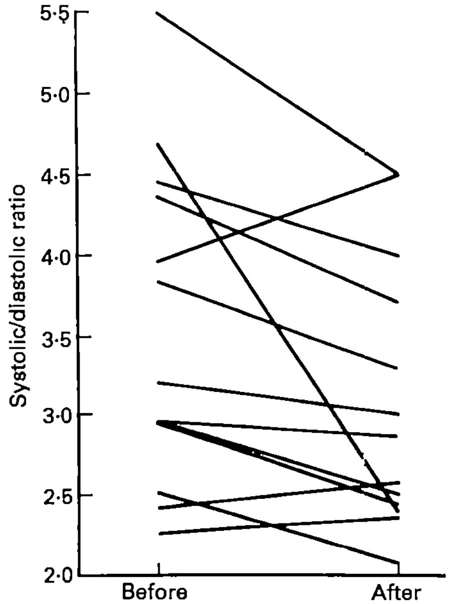

Fig. 4. Systolic/diastolic ratio before and after blood sampling only.

Discussion

Poiseuille's law states that an increase in viscosity produces an increase in resistance to flow and, indeed, Tenenbaum *et al.* (1983) increased blood viscosity and haematocrit by exchange transfusion in the sheep fetus and demonstrated a decrease in umbilical blood flow.

Jouppila *et al.* (1986) showed that umbilical vein blood flow was inversely related to blood viscosity and haematocrit in human pregnancies complicated by intrauterine growth retardation and hypertension while Giles *et al.* (1986) showed that fetuses exhibiting an abnormally high umbilical artery systolic/diastolic ratio had significantly higher haematocrit values than were found in an at-risk group with normal waveforms.

Doppler velocimetry has been used in pregnancies affected by rhesus isoimmunization to assess the need for fetal intravascular transfusion (Rightmire *et al.* 1986; Copel *et al.* 1988) but only one study has investigated the effect of intravascular transfusion on Doppler indices. Copel *et al.* (1988) showed a negative correlation between haematocrit and the umbilical artery systolic/diastolic ratio but did not include a group of patients who had blood sampling alone, and they concluded that this was of questionable clinical significance. We have shown that umbilical cord blood sampling is associated with a reduction in the systolic/diastolic ratio whether or not accompanied by intravascular transfusion. It is clear that the fetuses reported here were not representative of the polycythaemic, growth-retarded, chronically hypoxic fetus in which abnormal blood flow might be more likely, but nevertheless, we conclude that, under the conditions of our study, an increase in haematocrit is not associated with an increase in vascular resistance to flow as detected by Doppler velocimetry, and hypothesize that a humoral vasodilator, perhaps released from the endothelium at the time of umbilical cord puncture, may play a role in controlling fetal blood flow. While this hypothesis awaits further study, we suggest that our findings be borne in mind when umbilical velocimetry is being used to assess fetal well-being following umbilical blood sampling or transfusion.

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The action of squatting in the early postnatal period marginally increases pelvic dimensions

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Summary. X-ray pelvimetry was performed on 43 women in the squatting and erect positions within 1 week of delivery. The act of squatting increased the transverse and antero-posterior pelvic dimensions by 1%. The theoretical mechanisms by which posture may affect dimensions are discussed.

Squatting birth has been suggested to have many advantages (Gupta & Lilford 1987) although the only randomized trial comparing this method with a more conventional 'sitting' second stage failed because most of the patients assigned to squat were unable to do so (Gupta *et al.* 1989). One of the advantages claimed for squatting in the second stage of labour is that it enlarges pelvic dimensions. This claim has been made on theoretical grounds (Borrell & Fernstrom 1957*a*) and on the basis of direct radiological measurement of the inter-spinous distance (Young 1940; Borrell & Fernstrom 1957*b*; Russell 1969). We have attempted to examine the specific effect of squatting with respect to the erect position.

Patients and methods

Permission was obtained from 43 women, who were scheduled to have pelvimetry within 1 week after delivery, to obtain additional lateral and antero-posterior radiographs in the squatting position. The pelvic inlet was measured from the sacral promontory to the top of the symphysis pubis, the outlet from the tip of the fifth sacral vertebra to the bottom of the symphysis, and the bispinous diameter from the tips of each ischial spine. In order to make appropriate allowance for variable image magnification in the antero-posterior plane, dimensions were measured against a radio-opaque ruler which was inserted between the patient's buttocks before radiography. The true bispinous diameter was not adjusted. Each patient, standing and squatting, acted as her own control. The true bispinous diameter was recorded in unadjusted units from the radiograph.

Results

Good views of the ischial spines were obtained from all 43 patients in both squatting and standing positions. Although all women had recently been delivered by caesarean section they were all able to squat satisfactorily. The mean diameter was 12·99 (SD 1·0) units of measurement in the standing group increasing to 13·11 (SD 1·1) units on squatting—this change just reached statistical significance (P=0·047 with standard two-tailed paired t-test; P=0·050 with t-test on log-transformal data). The pelvic inlet (true conjugate) could be measured with accuracy in both positions in 30 subjects and showed an increase from a mean of 11·74 cm (SD 1·1) when standing to 11·87 cm (SD 1·1) when squatting (P=0·11 on log-transformal data). Similarly the outlet, measurable in 31 pairs, increased from 11·66 to 11·81 cm (P=0·13). The width of the symphysis pubis itself could not be measured with confidence

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Table 1. The effect of position on pelvic dimensions

	Diameter	
Position	Bispinous	A–P inlet
Standing	12·99 (1·0) units	11·74 (1·1) cm
Squatting	13·11 (1·1) units	11·87 (1·1) cm

Results are mean (SD) values.

because the margins of this joint were ill-defined radiologically (Table 1).

Discussion

We found very small changes in pelvic dimensions during squatting compared with the erect position in postpartum women. All measured dimensions increased as the patient squats by an order of 1% (1 unit which is approximately 1 mm). The resulting change in pelvic circumference would be an increase of 3 mm (πd) and the increase in area would be 2 cm^2. Moderate fetal moulding alters the fetal biparietal diameter by only 1–2 mm (4 mm in extreme cases) and small changes may be worthwhile. Nevertheless, the measurements were not 'blinded' since squatting could be inferred by the position of the femur and this or any other small systematic effect could account for the small difference which we detected. Standing and squatting both have similar effects and they are different (and superior) to those of sitting and lying (Gardosi 1988; Chen *et al.* 1987; Mendez-Bauer *et al.* 1975, 1976; Humphrey *et al.* 1974).

The pelvic ring is fairly rigid and contains only three joints, and there are therefore a limited number of mechanisms which could account for any increase in its dimensions. The possibility that the lower sacrum swivels backwards in a saggital plane, thus bringing the promontory forwards (rotation around horizontal coronal axis) would increase the diameter of the outlet at the expense of the inlet (Fig. 1) and this is not supported by previous data. The possibility (Fig. 2a) that the pelvic joints simply splay (widen) has been disproved radiologically (see review by Russell 1969). Russell seems to attribute his observed widening of the bispinous diameter to yet another mechanism: a backward hinge movement at the sacro-iliac joint with lateral rotation of the iliac bone (rotation around a vertical axis through the sacro-iliac joint) (Fig. 2b). This is, of course, the mechanism for more dramatic enlargement of the pelvis with symphysiotomy, and the appearance of gas in the symphyseal cartilage is cited as evidence for this mechanism in labour. Our observations, both of the bispinous diameters and of the symphysis, suggest that this effect is minimal, at least between standing and squatting, and we find it difficult to envisage much 'give' in the symphyseal cartilage. There is one remaining mechanism by which the pelvis may alter, especially in

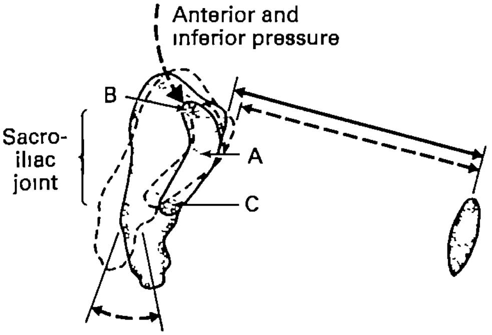

Fig. 1. One mechanism for enlargement of the lower saggital diameter of the pelvis involves rotation of the sacrum, around a horizontal and coronal (lateral) axis Backwards rotation of the sacral promontory around point A must enlarge the inlet at the expense of the outlet or *vice versa*. Force applied at point B, e.g. downward and forward pressure from the spine, would not cause rotation around point B, since any movement it produced would involve point B moving forward around a lower axis, e g. point A

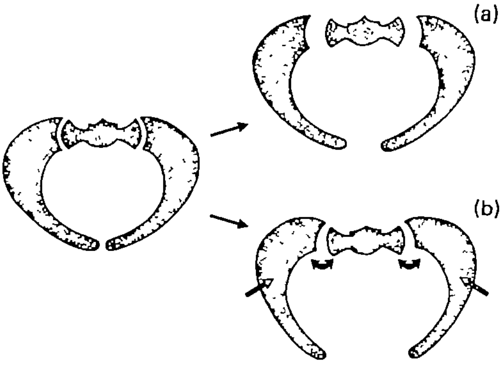

Fig. 2. Two further mechanisms for alteration in pelvic dimensions: (a) splaying (reverse moulding) of all joints is not supported by previous evidence, (b) hinge mechanism at the sacro-iliac joints—rotation around a vertical axis—a 'natural mini-symphysiotomy'. It is claimed that in the squatting position the femoral neck creates the necessary rotating force through the acetabulum The mechanisms in Figs 1 and 2b are not necessarily mutually exclusive

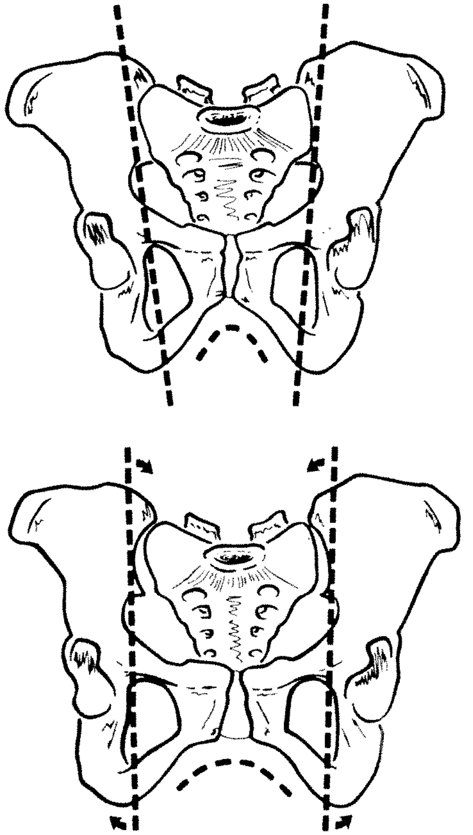

Fig. 3. Vertical and rocking movement of the ilium. This follows rotation around a saggital (antero-posterior) horizontal axis.

pregnancy. This is rotation around a saggital and horizontal axis through the sacro-iliac joint producing a vertical rotating movement of the ilium. This rotation reduces the distance between the superior-anterior iliac spines (and therefore transverse diameter of the 'false' pelvis) and enlarges that between the ischial spines and tuberosities (the transverse diameter of the true pelvis) (Fig. 3). Obviously this rotation is limited by the strong sacro-iliac ligaments and the topography of the sacro-iliac mortice. Nonetheless, appreciable widening of the transverse diameter of the pelvic outlet, with corresponding narrowing of the distance between the antero-superior iliac spines, will occur from a very small movement at the joint itself (the principle of levers). However, this mechanism would be difficult to establish radiologically because of the small rotational movements that are involved. In summary there are four mechanisms for changes in the pelvic dimensions: splaying or separation of all three joints or rotation at the sacro-iliac joints around horizontal and coronal, vertical or horizontal and saggital axes. These mechanisms are not necessarily mutually exclusive. We think that the act of squatting *per se* involves the last two mechanisms but we envisage that only limited movement is possible. Our results tend to confirm this but we eagerly await the results of measurements taken during pregnancy or even labour, possibly by magnetic resonance imaging or a vaginal ultrasound probe, and we will also compare the squatting and sitting positions.

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Oral contraceptive steroids and breast secretions

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Summary. Breast secretions were obtained by nipple aspiration from 164 (44·7%) of 368 consecutive premenopausal non-pregnant women volunteers attending family planning clinics. Women currently taking oral contraceptive steroids were significantly less likely to yield breast secretions than women who had never taken such preparations. The effect was confined to parous women of whom 94% not taking oral contraceptives yielded breast secretions compared with only 51% currently using the pill and 60% of those with a previous history of use. The percentage of nulliparous women yielding breast secretions (30%) was significantly less than that in parous women and was not affected by a present or previous history of contraceptive steroid use. These results provide further evidence of the difference in hormone responsiveness of parous and nulliparous breasts and the potential of oral contraceptive steroids to influence breast function.

Considerable interest exists in the relation between oral contraceptive steroids and breast disease, particularly breast cancer. Despite this, comparatively little is known about the effects of oral contraceptives on the function of the normal 'resting' female breast Secretion of breast fluids is typically associated with lactation but there is evidence that non-lactational, non-pregnant breasts also produce secretions (Keynes 1923, Sartorius 1973; Petrakis *et al.* 1975; Wynder *et al.* 1985). Histological examination of breasts at biopsy (Bonser *et al.* 1961) and autopsy (Sandison 1962) shows that many normal lobules and ductules contain secretion. Presumably these fluids are not normally expressed at the nipple because of resorption during passage through the duct system. However, competition with the resorption process by applying a negative pressure to the nipple can produce small beads of secretion at the outlets of one or more ducts in the breast (Sartorius *et al.* 1977). The present paper reports the effects of oral contraceptives and parity on the ability to obtain breast secretions from a population of premenopausal women attending family planning clinics.

Subjects and methods

All subjects were volunteers from three family planning clinics in the Edinburgh area over a period of 3 years. All women were premenopausal and had no breast abnormality or previous history of breast disease at the time of study. Women who had been pregnant or breastfed within 3 months of the study were excluded from the investigation. Attempts were made by one of two trained nurses, who did not know the clinical history of the subject, to obtain secretions from both breasts of each volunteer using a nipple cup consisting of two concentric rings (diameter of inner ring 1·7 cm, that of the outer ring 3 cm) as described by Sartorius (1973). This

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involved each volunteer massaging her breasts for 1 min by pushing inwards towards the nipple. The nipple was cleansed with a medi-swab immediately before application of the nipple cup attached via the inner ring to a 10-ml syringe The syringe was slowly drawn back through a 5-ml volume whilst the subject continued to compress her breast gently with both hands. This negative pressure was maintained for 15 s and the syringe finally drawn back to the final volume of 10 ml, this being maintained for 10 s. Subjects were classified as secretors if a visible bead of secretion appeared on the nipple of at least one breast; non-secretors failed to produce visible evidence of secretions from either breast The validity of using such an empirical classification has been discussed by Petrakis (1986).

Previous history of oral contraceptive use as recalled by the women was checked with the records of the family planning clinics and the nature of current oral contraceptive confirmed with the woman at the time of breast aspiration.

Statistical analysis was by χ^2-tests with Yates' correction and multiple logistic regression. *P* values <0·05 were regarded as significant.

Results

Of the 368 volunteers, only 31 women had never taken contraceptive steroids, 208 women were taking such preparations at the time of study (and had done so continuously for at least 3 months) and the remaining 129 subjects had used oral contraceptives previously but not in the 3 months immediately before the study (Table 1).

The overall frequency with which breast secretions were aspirated successfully was 44·6% (164 of 368 subjects) but as is shown in Table 1 the rate was influenced by the use of oral contraceptive steroids. Thus, whilst 67·7% of women who had never taken the contraceptive pill yielded secretions, only 35·1% of subjects who were currently taking such steroids produced breast secretions; the difference between the groups was highly significant. Those who had previously taken the oral contraceptive pill had an intermediate secretion rate which was not significantly different from the other groups of women.

As is shown in Table 2, parity also influenced the success rate of obtaining breast secretions. Nipple aspiration of parous women was twice as likely to produce secretions compared with that in nulliparous subjects (59·6% compared with 29·7%). Within the parous groups, number of pregnancies was not associated with any significant effect on secretor status.

Logistic regression analysis of secretor status on both parity and history of pill usage showed a significant interaction ($\chi^2 = 7·32$, d.f. 2, $P<0·05$) indicating that the trend in secretor prevalence with pill usage was different among parous and non-parous women. Thus among nulliparous women the use of contraceptive pills did not significantly affect secretor status, whereas amongst parous women both a present and previous history of oral contraceptives significantly reduced the success rate with which breast secretions were obtained. Indeed, whilst all but one parous subject without a history of contraceptive steroid use yielded secretions, successful aspiration was achieved in only about one half of women taking the pill at the time of study.

The decrease in frequency of breast secretions caused by contraceptive steroid use in parous women did not appear to be related to length of exposure in subjects currently using the pill or the interval free from the pill in those who were

Table 1. History of oral contraceptive (OC) use subdivided according to secretor status in the 368 women in the study

					Significance*	
OC use	No of women	Secretors	Non-secretors	(Per cent secretors)	χ^2	*P*
Never	31	21	10	(67·7)		
Ever	337	143	194	(42·4)	6·37	<0·05
Present	208	73	135	(35·1)	10·72	<0·005
Previous	129	70	59	(54·3)	1·34	>0·05
Total	368	164	204	(44·6)		

[*] Significance by χ^2-test compared with women never taking oral contraceptives (OC)

Table 2. The effect of parity and oral contraceptive (OC) use on secretor status

OC use	Secretors	Non-secretors	(Per cent secretors)	Significance* χ^2	Significance* P
Nulliparous women					
Never	4	9	(30·8)		
Ever	51	121	(29·7)	0·05	>0·05
Present	36	99	(26·7)	0.00	>0·05
Previous	15	22	(40·5)	0·09	>0·05
Total	55	130	(29·7)		
Parous women					
Never	17	1	(94·4)		
Ever	92	73	(55·8)	8·54	<0·001
Present	37	36	(50·7)	9·72	<0·01
Previous	55	37	(59·8)	6·54	<0·05
Total	109	74	(59·6)		

* Significance by χ^2-test compared with women never taking oral contraceptives (OC).

previous users (data not shown). As is shown in Table 3, the effects of oral contraceptives in parous women were not associated with age differences in the subjects, there being no significant differences in age between any subgroup of parous women. Whilst the nulliparous women were significantly younger than their parous counterparts, there were no statistically significant differences between subgroups either in terms of oral contraceptive history or secretor status. In any event, whilst age had a significant influence on secretor status when considered in isolation, multiple logistic regression analysis on probability of obtaining secretion showed that the effect of age could be fully accounted for by differences in parity and oral contraceptive history. In an attempt to define whether particular types of contraceptive steroids were responsible for these effects, two subgroups of women were identified amongst parous subjects taking oral contraceptives at the time of study: (i) women who had only been exposed to combination oestrogen–progestogen pills (for at least 6 months) and (ii) women who over the last 6 months had only taken progestogen-only preparations. These results are shown in Table 4 and suggest that oestrogen–progestogen pills are particularly associated with reduced occurrence of breast secretion. Thus in comparison with non-pill women, only the effect of the combination pill was statistically significant. However, progestogen-only preparations were still associated with a decreased rate of successful aspiration, and the percentage of secretors did not differ significantly between the two pill groups ($\chi^2 = 1{\cdot}98$).

Discussion

These results confirm that fluid may be obtained by nipple aspiration from the breasts of premenopausal women. The primary factors determining whether aspiration yielded secretion appeared to be parity and oral contraceptive use. Whilst it has been reported previously that parous women are more likely to be secretors than nulliparous subjects (Buehring 1979; Petrakis *et al.* 1981), the present study represents the first to indicate that contraceptive steroids and parity interrelate in determining the success with which breast aspirates may be

Table 3. Mean age in years (standard error of the mean) of the subjects subgrouped according to parity, oral contraceptive (OC) history and secretor status

Parity	OC history	Secretors	Non-secretors
Nulliparous	Never	29·8 (5·2)	24·2 (1·6)
	Present	24·6 (0·8)	25·6 (0·5)
	Previous	24·9 (1·1)	27·7 (1·3)
Parous	Never	38·3 (1·6)	49·0
	Present	32·8 (0·8)	30·6 (0·9)
	Previous	34·9 (0·9)	33·9 (1·1)

Table 4. The effects of different oral contraceptive (OC) pill preparations on secretor status in parous women

OC use	Secretors	Non-secretors	(Per cent secretors)	Significance*	
				χ^2	P
Never	17	1	(94·4)		
Oestrogen†–progestogen	16	21	(43·2)	11·18	<0·001
Progestogen alone	11	5	(68·8)	2·28	>0·05
Both	27	26	(50·9)	9·02	<0·01

* Significance by χ^2-test compared with women never taking oral contraceptives (OC)

† Apart from two subjects all women were taking low oestrogen preparations (30–35 mg ethinyloestradiol)

obtained. Earlier investigations have suggested that the frequency of successful aspiration from oral contraceptive pill users is lower than that from other women (Buehring 1979; Petrakis *et al.* 1981), but no comment has been made on potential interrelations between parity and contraceptive use.

However, results from the present study clearly indicate that not only do oral contraceptives reduce the occurrence of breast secretions but that the effect is restricted to parous women. Thus, whilst only approximately 30% of nulliparous women, irrespective of oral contraceptive use, were secretors, all but one parous subject with no history of oral contraceptives yielded breast secretion (interestingly, the single non-secretor at 49 years was the oldest woman in the group although still experiencing regular menstrual periods). The use of oral contraceptives, whether current or previous, significantly reduced the occurrence of breast secretions to 50–60% which was nevertheless still significantly higher than that in nulliparous women and suggests that contraceptive steroids were only capable of partially reversing the effects of parity. That a previous history in addition to current use of steroids was associated with reduction in secretions also suggests that either contraceptives are long-acting or their effects are relatively permanent. Such a relation between contraceptive steroids and parity has not been reported previously although evidence exists indicating that parity influences endocrine sensitivity of the breast (Drife *et al.* 1976; Masters *et al.* 1977; Battersby *et al.* 1988) and level of circulating hormones may differ between parous and nulliparous women (Bruning *et al.* 1984; Kwa *et al.* 1978).

Most of the women in the study were taking combination oestrogen–progestogen pills and it is therefore difficult to attribute effects to one or other steroid class. A small number were taking progestogen-only pills but analysis of the data is complicated by (a) the shorter time exposure of individuals taking progestogen-only pills compared with those using combination pills, and (b) the previous use of combination steroids by most of the women currently taking progestogen-only preparations. Nevertheless, there was a tendency for secretors to be over-represented in the group taking the progestogen pill; although this trend was not statistically significant, it is tempting to attribute the more marked effect of the combination pill to its oestrogen component.

The composition of breast secretions resembles that of both breast cyst fluid and apocrine sweat. All contain high concentrations of the androgen conjugate, DHA sulphate (Miller & Forrest 1983; Labows *et al.* 1979), and a distinctive protein, GCDFP-15 (Haagensen *et al.* 1979; Mazoujian *et al.* 1983), which seem to be markers of apocrine activity. It is therefore relevant that oral contraceptive use is associated with a decreased frequency of cysts within the breast (Pastides *et al.* 1983) and sweat (Royal College of General Practitioners 1974).

Whether these effects of oral contraceptives on secretor status have physiological or clinical importance can only be speculative. In view of the controversy surrounding oral contraceptives and risk of breast disease, the following comments may be pertinent and indicate that the finding could be used to support a mechanism in which oral contraceptives either increased or decreased risk. The case for decreased risk is as follows. Circumstantial evidence links apocrine activity within the breast with increased risk of breast cancer (Dixon *et al.* 1985), apocrine change being more commonly found in populations of women at high risk of breast cancer (Schuerch *et al.* 1982)

This would be compatible with the observation that Asian women who have a low risk of breast cancer (Gray *et al.* 1979) are less likely to produce nipple secretion than their Caucasian counterparts (Petrakis *et al.* 1975). Since breast secretion may act as a vehicle for mutagens (Petrakis *et al.* 1980), agents associated with non-secretor status might reduce the exposure of breast epithelium to potential carcinogens.

However, such considerations are undoubtedly an over-simplification because non-secretor status is not consistently associated with low risk of breast cancer and indeed may be related to high-risk groups. For example, nulliparous women who, as has been confirmed in this study, have a low occurrence of breast secretions, have an increased risk of breast cancer compared with parous women (Gillam 1951; Logan 1953). Furthermore, if oral contraceptives did not inhibit the production of breast fluids but rather interfered with their expression at the nipple by, for example, producing resorption through ductal epithelium, this might result in increased exposure to harmful constituents of breast secretion.

It is clear therefore that greater understanding of the physiology of the resting breast and the role of breast secretions is required before a more definitive statement can be made concerning the clinical significance of the changes associated with oral contraceptive steroids as observed in this study.

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A randomized controlled trial of extra-amniotic ethinyloestradiol in ripening the cervix at term

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Summary. A double-blind randomized controlled trial investigated the use of extra-amniotic ethinyloestradiol for ripening the unfavourable cervix at term. Twenty-five primigravidae were treated with 150 mg ethinyloestradiol gel while 24 primigravidae were treated with gel alone. There was no statistical difference between the ethinyloestradiol and control groups in either mean change in Bishop score or the induction-to-delivery interval.

We have been searching for a simple, safe, effective and inexpensive method to induce labour. The unripe or unfavourable cervix in late pregnancy presents a difficult clinical problem if labour needs to be induced. With an unripe cervix, induction of labour with amniotomy and oxytocin is associated with increased occurrences of epidural analgesia, caesarean section, forceps delivery, episiotomy, prolonged labour, maternal and fetal infection and fetal asphyxia (Bishop 1964; Smith *et al.* 1984).

A wide variety of methods of cervical ripening has been described including intravaginal oestradiol gel (Tromans *et al.* 1981), extra-amniotic oestradiol gel (Gordon & Calder 1977; Thiery *et al.* 1978; Gordon 1981; Stewart *et al.* 1981) and extra-amniotic oestriol gel (Thiery *et al* 1978; Quinn *et al.* 1981) However, the ripening properties of oestradiol could not be confirmed in two studies (Thiery *et al.* 1978; Pedersen *et al.* 1981), and oestradiol given intramuscularly seemed not to affect subsequent induction of labour with prostaglandins (Luther *et al.* 1980) In view of the uncertainty about the value of oestrogens, this study was designed to test the hypothesis that extra-amniotic oestradiol ripened the unfavourable cervix at term.

Subjects and methods

The study included 50 primigravidae at over 37 weeks gestation who were scheduled to have labour induced for various reasons. The sample size (25 in each group) was calculated using the results of Gordon & Calder (1977). Type I error was taken to be 0·05, Type II error as 0·01 (power of the test = 0·99) and the clinically significant difference in Bishop scores as 2·0. All the women gave informed consent to participation in the study. Inclusion criteria were: singleton pregnancies with cephalic presentation, gestational age over 37 weeks and a modified Bishop score (Calder *et al* 1974) of $\leqslant 3$. Women who had any contraindication to induction such as contracted pelvis and uterine scar were excluded. Also excluded were those who had conditions that could affect the induction-to-delivery interval: fetal anomaly, premature rupture of membranes, false labour and patients who had had stripping of the membranes.

Preparation of the gel

Ethinyloestradiol powder was dissolved in arachis oil at 70°C. The viscous solution so obtained was made available in amber-coloured

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ampoules each containing 5 ml of gel with 150 mg of ethinyloestradiol. Placebo gel consisted of only arachis oil similarly treated so as to be of identical colour, consistency and smell; 25 ethinyloestradiol and 25 placebo ampoules were prepared. They were numbered at random from 1 to 50 and the code kept only with the hospital pharmacy department

Pre-induction treatment

On the eve of induction, the patient was taken to the labour room at about 20.00 hours, and if the criteria for the study were fulfilled, treatment was initiated. Cervical scoring used the modified Bishop score. A No. 16 Foley catheter was introduced through the cervical os to a length of 10 cm. A bivalved speculum and a no-touch technique were used to ensure asepsis. The catheter bulb was inflated with 10 ml of water and the catheter pulled back so that the bulb hitched against the internal os. The serially numbered ampoules were used in sequence. The gel was introduced into the extra-amniotic space through the catheter with a syringe. The catheter was tied and left *in situ* till the following morning. The patient was sent back to the antenatal ward after 30 min Uterine activity was recorded with scores from 0 to 3 (Quinn *et al* 1981).

Induction

At about 08.00 hours the next morning, 12 h after instillation of the gel, the patient was given an enema and taken to the labour room. The catheter was now removed if it had not fallen out spontaneously. Pelvic examination and cervical scoring were repeated. Forewater amniotomy was then performed and oxytocin infusion begun for all patients. All the cervical scoring, instillation of the gel and amniotomies were done by one investigator (A.P.).

The oxytocin infusion (gravity drip method) was monitored clinically. The rate of the drip was increased till three contractions lasting for 40–45 s every 10 min were obtained. A uniform method of oxytocin infusion was ensured by following a protocol of increasing the drip rate in arithmetical progression every 15 min if contractions were inadequate.

Prophylactic antibiotic cover with three doses of ampicillin was given. Sedation was given every 4–6 h at the obstetrician's discretion. Decisions about obstetric interventions for fetal distress or failure to progress were made by the consultant in charge of the patient

Analysis

On completion of the trial, the code was finally broken to determine the placebo and the ethinyloestradiol groups. Analysis was performed by Student's t-test and the χ^2-test.

Results

Comparability of patient groups

There were 25 patients in the ethinyloestradiol group (E_2 group) and 24 patients in the control group since one of the ampoules was accidentally broken. Table 1 shows that the two groups were comparable in clinical features and indications for induction

Ripening effects

Both the E_2 and control groups showed a definite change in Bishop score, 3·04 and 2·58 respectively. This difference was not statistically significant ($P>0{\cdot}05$). The maximum change occurred in dilatation and effacement of the cervix (Table 2). Most patients slept after catheter insertion as reflected by the uterine activity score.

Outcome of induction

There were no significant differences between the two groups in the latent period, induction-to-delivery interval, quantity of oxytocin and pethidine required, blood loss at delivery or the Apgar scores (Table 3). The mode of delivery is shown in Table 4. In the E_2 group one woman went into labour during the preparation phase; 13 were delivered spontaneously, 10 by either forceps or suction-cup and two by caesarean section. One caesarean section was for fetal distress and one for brow presentation that was not detected when the gel was inserted. In two women the protocol was broken and oxytocin was discontinued after 15 h induction. These two patients were delivered vaginally the following day after oxytocin was restarted.

In the control group there were 14 spontaneous deliveries, five instrumental deliveries and five caesarean sections One section was for

Table 1. Clinical features and indications for induction in the two study groups

	Oestradiol (n=25)		Control (n=24)	
	Mean	(SD)	Mean	(SD)
Clinical features				
Age (years)	22·76	(3·54)	23·38	(3·8)
Height (cm)	153·56	(5·7)	153·42	(7·63)
Weight (kg)	58·58	(8·06)	59·81	(9·07)
Gestational age (weeks)	40·42	(1·21)	40·11	(1·53)
Initial Bishop score	2·28	(0·74)	2·21	(0·83)
Birthweight (kg)	2·76	(0·26)	2·8	(0·39)
Indication for induction				
Postmaturity	11		6	
Pregnancy-induced hypertension	12		12	
Intrauterine growth retardation	—		5	
Decreased fetal movements/non-reactive non-stress test	2		1	

fetal distress, two for failure to progress and two for cephalopelvic disproportion.

Complications

Failed induction was defined as labour lasting >24 h (two women in whom oxytocin was discontinued overnight) or caesarean section (7 women). Only three women in each group had fever which was low grade. There were no accidentally ruptured membranes or deliveries during the preparation phase.

In the E_2 group two babies had a 1-min Apgar score of <5 and in one baby gestational age was 36 weeks. In one woman in whom oxytocin was discontinued overnight, *Escherichia coli* grew in neonatal blood cultures. Neonatal hyperbilirubinaemia (>10 mg/dl) was seen in three babies. There were no perinatal deaths or other complications in either of the two groups.

Discussion

Oestrogens are believed to 'unlock the door' while prostaglandins 'storm the gate' of the cervix (Beazley & Lobb 1983). Oestradiol modulates glycosaminoglycan synthesis and increases formation of prostaglandins and their receptors

Table 2. Cervical ripening in the two study groups

	Oestradiol (n=25)		Control (n=24)			
Factors	Mean	(SD)	Mean	(SD)	Difference between means	95% CI
Initial Bishop score (pre-gel)	2·28	(0·74)	2·21	(0·83)	0·07	−0·38 to 0·52
Dilatation	0·16	(0·37)	0	(0)	0·16	−0·002 to 0·3
Effacement	1·0	(0·58)	1·0	(0·72)	0	−0·37 to 0·37
Consistency	1·08	(0·28)	1·25	(0·44)	−0·17	−0·46 to 0·12
Position	0	(0)	0·04	(0·2)	−0·04	−0·12 to 0·04
Station	0·04	(0·2)	0·04	(0·2)	0	−0·11 to 0·11
Final Bishop score (post-gel)	5·32	(1·99)	4·79	(1·59)	0·53	−0·5 to 1·56
Dilatation	1·76	(0·6)	1·54	(0·59)	0·22	−0·12 to 0·56
Effacement	1·68	(0·75)	1·58	(0·72)	0·1	−0·32 to 0·52
Consistency	1·36	(0·49)	1·38	(0·5)	−0·02	−0·3 to 0·26
Position	0·32	(0·48)	0·17	(0·38)	0·15	−0·1 to 0·4
Station	0·16	(0·47)	0·13	(0·34)	0·03	−0·21 to 0·27
Mean change in Bishop score	3·04	1·84	2·58	1·44	0·46	−0·49 to 1·41
Uterine activity	0·36	0·7	0·33	0·57	0·03	−0·34 to 0·4

Table 3. Outcome of induction

Factors	Oestradiol *n*	Oestradiol Mean	Oestradiol (SD)	Control *n*	Control Mean	Control (SD)	Difference between means	95% CI
Latent period (h)*	24	1·59	(1·63)	24	1·31	(1·57)	−0·22	−1·44 to 0·7
Induction-to-delivery interval (h)†	20	8·53	(3·46)	19	7·36	(3·43)	0·67	−1·56 to 2·9
Oxytocin infused (units)†	20	7·12	(4·8)	19	7·79	(4·94)	−0·67	−3·82 to 2·48
Pethidine (mg)†	20	83·7	(40·7)	19	93·4	(57·6)	−9·67	−41·8 to 22 5
Blood loss (ml)	25	186·0	(91·8)	24	181·3	(111·4)	4·75	−53·5 to 63·0
Apgar score at 1 min	25	8·04	(1·27)	24	8·75	(0·79)	−0·71	−1·32 to −0·1
Apgar score at 5 min	25	9·8	(0 41)	24	9·92	(0·28)	−0·12	−0·25 to 0·01

*Excluding a patient with onset of labour during preparation phase.

†Excluding women delivered by caesarean section, those with onset of labour during preparation phase and in whom oxytocin was discontinued

(Liggins 1983; Uldbjerg *et al.* 1983). Prostaglandin E_2 (Calder & Embrey 1973; Shepherd *et al.* 1976; Calder *et al.* 1977) and $PGF_{2\alpha}$ (Quinn *et al.* 1981) gels have also been used in the extra-amniotic route. The postulated advantages of oestrogens over prostaglandins are that labour rarely becomes established during the ripening period, there is a relative lack of uterine stimulation, and oestrogens may be used even if there is some bleeding on insertion of the catheter (Gordon & Calder 1977; Stewart *et al.* 1981).

Both groups in our study showed a definite change in Bishop score although oestradiol did not ripen the cervix any more than an extra-amniotic Foley catheter. There is a likelihood of Type II errors when sample size is small. However, the sample size used in this study was calculated keeping Type II error at 0·01. The standard deviation of Bishop scores in the two groups as well as the improvement in Bishop score in the control group were greater than those obtained by Gordon & Calder (1977).

The latent period and induction-to-delivery intervals were similar and shortened in both groups. With conventional methods of induction, labour is 5 to 6 h longer (Wilson 1978; Varma & Giannacodimos 1984). Taking both groups together, the caesarean section rate was only 14% which is identical to the overall section rate for our hospital. The induction failure rate of 18% is far less than the 25–50% failure in patients with unfavourable cervical scores who are induced by conventional methods (Hughey *et al.* 1976; Wilson 1978). Pedersen *et al.* (1981) reported an association between the use of extra-amniotic oestradiol and neonatal hyperbilirubinaemia. Three babies in our study had neonatal jaundice, but none required therapy One baby had evidence of infection (*E.coli* grown in blood culture), but maternal oxytocin had been discontinued overnight and started again the next day. When the catheter is inserted aseptically, infection is rare (Callen *et al.* 1980).

Table 4. Mode of delivery and complications

	Oestradiol (*n*=25)	Control (*n*=24)	Relative risk	95% CI
Spontaneous delivery	13	14	0·89	0·54 to 1·48
Instrumental delivery	10	5	1 92	0·77 to 4·8
Failed induction	4	5	0·77	0·23 to 2·53
Caesarean section	2	5		
Labour > 24 h	2	0		
Maternal pyrexia	3	3	0·96	0·21 to 4·3
Apgar score at 1 min < 5	2	0	—	—
Inadvertent preterm	1	0	—	—
Neonatal sepsis	1	0	—	—
Neonatal hyperbilirubinaemia (> 10 mg/dl)	1	2	0·48	0 05 to 4·92

The Foley catheter has been shown to ripen the cervix effectively (Embrey & Mollison 1967; Ezimokhai & Nwabineli 1980; Sandhu & Tung 1984), and at term it seems to be efficacious without the additional use of oestradiol. The catheter probably brings about the ripening by promoting the release of prostaglandins from the fetal membranes. To minimize the catheter effect the bulb was inflated to only 10 ml as in an earlier study (Quinn *et al* 1981). The low complication and failure rates and the additional advantage of low cost are particularly appealing.

This study failed to show that ethinyloestradiol is a more effective cervical ripener than an extra-amniotic Foley catheter. Both groups evidenced cervical ripening and satisfactory outcomes to induction of labour.

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Neutrophil activation in pregnancy-induced hypertension

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Summary. Human neutrophil elastase may be a major mediator of vascular damage and could contribute to the vascular damage seen in women with pregnancy-induced hypertension (PIH). Elevated plasma levels of this substance will reflect neutrophil activation *in vivo*. To determine neutrophil activation in PIH, we studied 30 normal non-pregnant women, 32 women with normal pregnancies, 19 with mild/moderate PIH and 16 with severe PIH between 28 and 39 weeks gestation. Plasma neutrophil elastase was measured by radioimmunoassay. There was a significantly higher concentration of plasma neutrophil elastase in both mild/moderate and severe PIH than in normotensive pregnancies and this may contribute to the vascular lesion associated with PIH. Concentrations were also significantly higher in normal pregnancy than in non-pregnant women which suggests that neutrophil activation and degranulation are increased in normal pregnancy.

Pregnancy-induced hypertension (PIH) remains a leading cause of maternal mortality in the UK (DHSS 1986) and is a major source of perinatal mortality and morbidity. Its precise aetiology remains obscure, but it is characterized by increased vascular reactivity (Gant *et al* 1973), platelet activation, coagulation changes (Howie 1977) and vascular damage (Robertson & Khong 1986). This last feature has been termed acute atherosis and can be seen in the utero-placental bed of women with PIH (Zeek & Assali 1950; Dixon & Robertson 1958) where the small muscular arteries in the decidua and myometrium undergo acute fibrinoid necrosis with destruction of the vascular tissue and deposition of fibrin. The pathogenesis of this necrotizing arteriopathy is unknown, but haemodynamic factors secondary to the hypertension (Robertson *et al.* 1967) and inappropriate immune reactions (Kitzmiller & Benirschke 1973) have been suggested as possible triggers. Recently, neutrophils have been implicated in the pathogenesis of vascular damage in the non-pregnant (Harlan 1987). Activated neutrophils release a variety of substances which are capable of mediating vascular damage. These include the contents of neutrophil granules such as elastase and other proteases which can destroy the integrity of endothelial cells, vascular basement membrane and subendothelial matrix (Harlan 1987). In

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addition, toxic oxygen radicals are released which can result in membrane lipid peroxidation, lysis of endothelial cells, disruption of the endothelium and increased vascular permeability and reactivity (Harlan 1987). Leukotrienes, products of arachidonic acid metabolism in white cells, are also synthesized and released following white cell activation and they too will increase vascular permeability, induce vasoconstriction and promote further neutrophil activation and adherence (Bray 1983).

Neutrophil elastase may be a major mediator of vascular damage and could contribute to the vascular lesion seen in PIH. Its concentration in human plasma is normally very low, and elevated levels reflect neutrophil activation and degranulation *in vivo* (Weissman *et al.* 1980). The aim of this study was to measure plasma neutrophil elastase in the peripheral circulation of women with PIH and to compare this with uncomplicated pregnancies and non-pregnant women to determine whether neutrophil activation, which could contribute to the vascular damage seen in PIH, occurs in this disorder.

Subjects and methods

Thirty normal healthy non-pregnant women were studied as a non-pregnant control group; they were randomly selected from female laboratory staff and were a mixture of smokers and non-smokers; their mean age was 26·3 (SD 6·2) years. The 67 pregnant women in the study were in the third trimester; 32 had uncomplicated pregnancies, 16 had severe PIH and 19 had mild/moderate PIH. Severe PIH was defined as a persistent elevation of diastolic blood pressure >90 mmHg with proteinuria (>0·3 g/24 h). Mild/moderate PIH was defined as a persistent elevation of diastolic blood pressure >90 mmHg without proteinuria. All patients were normotensive in the first trimester. All groups were sampled between 28 and 39 weeks gestation, and the PIH groups were sampled after diagnosis but before any anti-hypertensive therapy. Peripheral venous blood was obtained and anticoagulated with 3·2% trisodium citrate. This was then centrifuged for 10 min at 3000 rev/min at 4°C within 60 min of venepuncture and the plasma separated and stored at −20°C.

Any patient with clinical or laboratory evidence of infection was excluded as infection will result in increased neutrophil activity. Laboratory exclusions included a white cell count of >12 000/mm^3 as this may represent a subclinical infection.

Human neutrophil elastase was measured by specific radioimmunoassay using rabbit polyclonal antiserum raised in house. The antigen was purified from human neutrophils following leukapheresis, and was a kind gift of Dr P. Davies (Merck, Sharp & Dome). The antibody was absolutely specific for neutrophil elastase; it did not cross-react with pancreatic or platelet elastases, but measured neutrophil elastase equally well as the free enzyme or as complex with its inhibitors, α_1-antitrypsin and α_2-macroglobulin. The antibody was tested against neutrophil-free lysed platelet concentrate and against pancreatic elastase (Sigma) and no cross-reactivity occurred. In addition, human neutrophil elastase was incubated with α_1-antitrypsin and α_2-macroglobulin (Sigma), with these inhibitors present in excess, and 100% recovery of elastase was obtained using the assay. In brief, 50 µl of standard/sample were added to 50 µl ^{125}I-elastase (10 ng/ml) and 50 µl anti-elastase antibody (dilution 1:3000) and made up to 200 µl with buffer comprising 0·05 M phosphate (pH 7·4), 0·6 M NaCl, 2 mM EDTA, 130 mg/ml heparin, 20 u/ml aprotinin and 2% heat-inactivated horse serum. Samples were incubated overnight at room temperature and separated with donkey anti-rabbit immunoglobulin immobilized on Sepharose. After shaking for 45 min at room temperature, the bound complex was separated from the free complex by sedimentation under gravity through a 10% sucrose solution, then aspirated and counted on a NE 1600 gamma counter. Plasma neutrophil elastase was expressed in ng/ml.

Statistical methods

Plasma neutrophil elastase measurements were compared using a z-test following $\log_{10}$ transformation of the data. Age, gestation at time of sample and gestation at delivery were compared using Student's t-test for unpaired data. Fisher's exact test was employed to compare the primigravid:parous ratio and smoking habit between the groups

Results

The details of the pregnant patient groups and outcome are given in Table 1. There were no significant differences between the three preg-

Table 1. Characteristics of the pregnant women in the study†

	Normotensive (n=32)	Mild/moderate PIH (n=19)	Severe PIH (n=16)
Mean age (years) (SD)	24·6 (5·9)	28·8 (5·5)	24·8 (4·5)
Primigravida	18	15	12
Number of smokers	8 (25%)	3 (16%)	3 (19%)
Mode of delivery			
Caesarean section	2 (6%)	8 (42%)	9 (56%)
Forceps	3 (9%)	8 (42%)	5 (31%)
Spontaneous vaginal	27 (85%)	3 (16%)	2 (13%)
No with birthweight ≤10th centile	0	0	7 (44%)
Gestation (weeks)			
At delivery Mean (range)	39·8 (37–42)	39·0 (36–41)	34·4 (28–39)*
At sampling Mean (range)	34·2 (28–39)	35·2 (30–39)	33·0 (28–38)

* $P<0·001$.

† A non-pregnant control group of 30 women was studied; their mean age was 26·3 (SD 6·2) years and about 60% were non-smokers.

nant groups in terms of age, gestation at time of sample, parity or smoking habit. The mean gestation at delivery was significantly shorter in the severe PIH group than in the other two groups and there were substantially more operative deliveries in the PIH groups. In the severe PIH group, 44% of the infants were below the 10th centile of weight-for-gestation but there were no instances in the mild/moderate group. There was one neonatal death in the study. This was a small-for-gestational-age infant born at 28 weeks by caesarean section in a patient with severe PIH. The infant died in the first weeks of life from the complications of prematurity and low weight.

The plasma neutrophil elastase results are shown in Fig. 1. There was a significantly higher concentration of plasma neutrophil elastase in both the severe ($P<0·002$) and the mild/moderate ($P<0·001$) PIH groups compared with the pregnant normotensive control group. In addition, the concentration was significantly higher in the normal pregnant group than in the normal non-pregnant group ($P<0·001$).

Discussion

Neutrophil elastase is released from the azurophilic granules of granulocytes following cell activation. The polyclonal antiserum used in this study against purified human neutrophil elastase did not bind to any other neutrophil protein, and did not detect the antigenically distinct elastases from platelets and pancreas. It did, however, measure neutrophil elastase equally well in the free form and when complexed to its inhibitors α_1-antitrypsin and

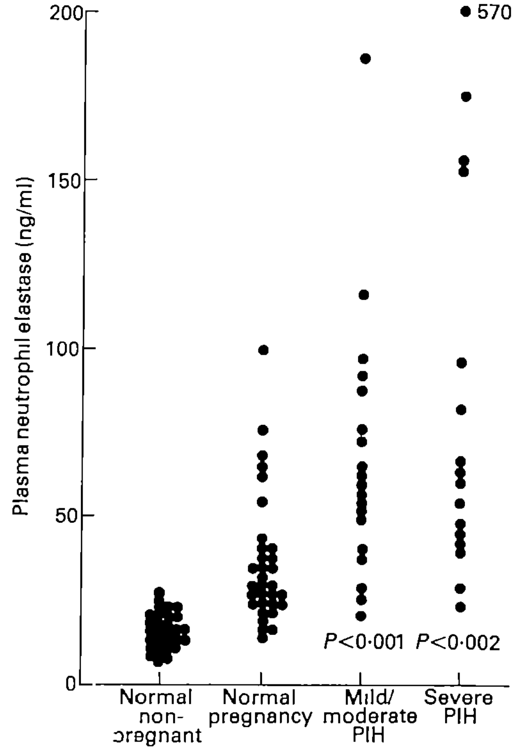

Fig. 1. Plasma neutrophil elastase concentration (ng/ml) in normal non-pregnant women, normal third trimester pregnancies and in pregnancies complicated by mild/moderate and severe PIH.

α_2-macroglobulin, the forms in which it circulates in plasma. Thus measurement of plasma elastase provides a marker for neutrophil activation and granule release *in vivo*. Since there is no correlation beween peripheral neutrophil count and plasma neutrophil elastase, any increase in elastase must reflect increased neutrophil activation (Janoff 1985).

This study is the first to demonstrate that plasma neutrophil elastase is elevated in PIH and indicates that white cell activation and degranulation occur in this disorder. This may account for the vascular lesions seen in PIH such as those noted in the placental bed (Robertson & Khong 1986). Neutrophil elastase can cause substantial tissue damage as its substrates include not only elastin, but also collagen, fibrinogen, complement and proteoglycans (Janoff 1985). Other neutrophil granule constituents which are released along with elastase include cationic proteins which increase vascular permeability (Janoff & Zweifach 1964), and acid and neutral proteases which can destroy vascular basement membrane (Harlan 1987) The reactive oxygen species which are also released by activated neutrophils are potent mediators of cell injury. They will produce membrane lipid peroxidation, lysis of endothelial cells, cell retraction, increased vascular permeability and vasoconstriction (Sacks *et al.* 1978; Weiss *et al.* 1981). In addition, leukotriene generation by neutrophils will amplify the response by increasing neutrophil adherence to vascular tissue and will also promote increased vascular permeability (Harlan 1987; Bray 1983). When neutrophils adhere to endothelium a 'protected microenvironment' (Harlan 1987) obtains at the interface between neutrophil and endothelial cell so that neutrophil granule proteases can degrade the vascular tissue while being inaccessible to plasma protease inhibitors such as α_1-antitrypsin and α_2-macroglobulin. Thus is can be seen that activated neutrophils may contribute directly to the vascular damage seen in PIH as well as interacting with the platelet, coagulation and complement systems which are activated in PIH. The activation of neutrophils in PIH is likely to be a secondary phenomenon, possibly triggered by immunological mechanisms which have been implicated in the aetiology of this disorder (Stirrat 1986). Nonetheless, it may be an important contributor to the pathogenesis of this disease.

It is noteworthy that the concentrations of elastase were not significantly different in mild/moderate and severe disease, so that there was no correlation with disease severity as judged by the presence of proteinuria, which is an established indicator of severe disease. This suggests that neutrophil activation may occur early in the disease process producing vascular damage which can lead to placental insufficiency as well as renal damage in susceptible patients.

It is interesting that neutrophil granule enzymes (Miller *et al.* 1985), reactive oxygen species (Ager & Gordon 1984) and leukotrienes (Pologe *et al.* 1984) have been shown to stimulate prostacyclin release from endothelial cells. This seems paradoxical as PIH is associated with a deficiency of prostacyclin production (McLaren *et al.* 1987; Greer *et al.* 1986; Goodman *et al.* 1982) which is thought to contribute to the platelet consumption and vasoconstriction of PIH. However, the stimulation of prostacyclin release found *in vivo* in response to these stimuli is likely to be a transient response to the initial damage It is known that at low concentrations reactive oxygen species can stimulate cyclo-oxygenase, an enzyme essential for prostacyclin production, but at higher levels inhibit both this enzyme and prostacyclin synthase (Warso & Lands 1983). Furthermore, high concentrations of reactive oxygen species can reorientate the arachidonic acid pathway in the cell away from the production of the cytoprotective and vasodilator agent prostacyclin towards thromboxane A_2 (Warso & Lands 1983) which is a potent stimulator of platelet aggregation and vasoconstriction. Thromboxane A_2 production is also known to be increased in PIH (Wallenberg & Rotmans 1982). Thus neutrophil activation may account for the necrotizing arteriopathy seen in PIH which hitherto has been poorly explained, and also for several other features of the disease such as prostacyclin deficiency and enhanced thromboxane production.

The increased concentrations of plasma neutrophil elastase in normal pregnancy as compared with the non-pregnant group suggest that neutrophil activation is increased in the normal situation. Neutrophils have cellular responses similar to those of platelets (O'Flaherty *et al.* 1979). It is known that platelet reactivity is enhanced in normal pregnancy (Morrison *et al.* 1985, Burgess-Wilson *et al.* 1986) and that this is exaggerated in PIH. The mechanism behind this increased reactivity is unclear; however, in view of the similarities between neutrophil and platelet cellular responses, there may be a common mechanism enhancing the reactivity of both cell types in normal pregnancy. Within the third trimester there were no obvious effects of gestational age on plasma elastase concentration, but a longitudinal study is required to study this further, and to determine at what stage in pregnancy neutrophil activation increases

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The Stamey operation for correction of genuine stress incontinence in the elderly woman

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Summary. Forty-four elderly women underwent the Stamey procedure for urethral sphincter incompetence; six had coincidental detrusor instability. All had pre- and postoperative urodynamic assessment. At follow-up, 15 patients continued to complain of stress incontinence and 11 of urge incontinence. Overall, 27 patients still had objective evidence of genuine stress incontinence, and 15 had evidence of detrusor instability. Although the operation has minimal operative and postoperative morbidity, we do not consider its success rate satisfactory for use in the elderly.

Stamey advocated an endoscopic bladder neck suspension for all patients with genuine stress incontinence, and reported 93% cure of genuine stress incontinence (Stamey *et al.* 1975). Mundy (1983) compared the Stamey procedure with a colposuspension for the treatment of genuine stress incontinence and found an objective cure rate of 40% for the Stamey procedure and 73% for the colposuspension. However, the author noted the Stamey procedure was quicker, simpler and a lesser procedure which therefore might have a very definite role in the elderly or unfit patient because of its anticipated lower postoperative morbidity and relatively pain-free convalescence. In addition, many elderly women have a significant reduction of vaginal capacity and mobility, rendering it difficult to perform a colposuspension, and therefore the Stamey operation might be the more appropriate procedure.

This prospective study assesses the morbidity and results of the Stamey procedure for elderly women with urodynamically proven genuine stress incontinence.

Patients and methods

Our indication for the Stamey procedure was genuine stress incontinence in the elderly patient (age 65 years or more) without significant uterine descent. Six patients had mild detrusor instability. From January 1985, 44 patients aged 65–94 years had 46 Stamey operations All were assessed pre-operatively with a urodynamic questionnaire, clinical examination, twin-channel subtracted cystometry (CMG) or videocystourethrography (VCU), lateral chain cystography and a Urilos or pad test

The Stamey operation (Stamey *et al.* 1975) consists of insertion of a nylon suture using a Stamey needle, via a 3-cm suprapubic incision to one side of the midline, to exit just medial to the bladder neck, at a previously prepared anterior vaginal wall incision. The nylon suture is threaded through a 1-cm Dacron or Silastic buffer and the suture is then passed suprapubically, 1 cm lateral to the previous insertion, at the level of the bladder neck, to form a loop. The suture is then passed through a further buffer. This manoeuvre is repeated on the other side of the bladder neck. The patient is then cystoscoped to ensure the sutures are at the

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Table 1. Urodynamic data before and 3 months after a Stamey procedure in 44 women with genuine stress incontinence*

	Patient category (post-op. assessment)*					
	Dry ($n=17$)		Wet ($n=27$)		Total ($n=44$)	
	Pre-op.	Post-op.	Pre-op.	Post-op	Pre-op.	Post-op.
Mean age (years)	74·8	—	73·5	—	74	—
Mean weight (kg)	64·5	—	67·2	—	64·9	—
Parity						
Nulliparous	4	—	4	—	8	—
>2 births	4	—	13	—	17	—
Bladder neck surgery						
None	10	—	11	—	21	—
>2 operations	0	—	2	—	2	—
Symptoms						
Frequency	11	5	20	8	31	13
Stress incontinence	4	1	23	13	27	14
Urgency	8	12	18	19	26	31
Urge incontinence	6	8	15	16	21	24
Voiding difficulty	4	2	8	4	12	6
Signs						
Cystourethrocele (marked)	2	0	1	0	3	0
Rectocele (marked)	0	0	2	2	2	2
Stress incontinence	5	0	19	7	24	7
Positive urodynamic findings						
Peak flow rate <15 ml/s	3	6	5	8	8	14
Detrusor instability	3	7	2	8	5	15
Genuine stress incontinence	15	0	23	26	38	26
Positive pad test	3	0	3	13	6	13

* Patient category 'Dry' or 'Wet' was based on objective findings at 3 months follow-up after the operation.

level of the bladder neck and that the bladder has not been breached. The anterior vaginal wall incision is closed. When the sutures are individually tied, paraurethral tissue and rectus sheath are approximated and the bladder neck is thus elevated. To determine how much suture tension is necessary, Stamey *et al.* (1975) took bladder neck closure on endoscopy when tying the supporting sutures as the correct end-point. Abrams (1988) and Mundy (1983) relied upon interruption of a jet of water from a full bladder. We chose to comfortably elevate each lateral fornix using a finger in the vagina, and tied the corresponding suture to maintain this position, rather like the technique for a colposuspension.

A suprapubic catheter was inserted and a note made of the duration of surgery from the vaginal incision to this point Blood loss and surgical complications were recorded.

The surgery was performed by one of the team always under consultant supervision. Metronidazole, 1 g per rectum, and cephradine, 500 mg intramuscularly, were given with the premedication. Postoperatively the suprapubic catheter was managed as described previously (Stanton 1984). Patients were mobilized from the first postoperative day. Postoperative complications and a note of the total amount of analgesia were recorded.

At the 3-month follow-up all patients were reviewed with history, clinical examination, peak flow rate, CMG or VCU, pad test and lateral chain cystography. If stress incontinence was demonstrable clinically or at CMG or VCU, or if the pad test was positive, the patient was considered to be objectively wet. Follow-up was to continue at yearly intervals for 3 years. Unless otherwise mentioned, definitions are those spec-

Table 2. Operative and postoperative data associated with 46 Stamey procedures in 44 women

Surgical time (min) Mean (range)	32 (21–65)
No. with blood loss >300 ml	3
Sutures cut through	
Bladder neck elevated	2
Bladder neck not elevated	3
Postoperative complications	
Pyrexia*	3
Urinary tract infection	14
Wound infection	1
Haematoma	3
Voiding difficulty	1
Suture in bladder	1
Days to removal of catheter	
Mean (range)	6·6 (3–22)
Mean dose of analgesia	
Papaveretum (mg)	27·6
Pethidine (mg)	123·7
No. of dihydrocodeine and paracetamol tablets	17
Post-op. days in hospital Mean (range)	10·4 (6–29)

* Pyrexia >38°C for ≥24 h

ified by the International Continence Society (1980).

Results

The results at 3-month follow-up are presented in Table 1. For analysis, the patients were divided into two groups according to whether incontinence was objectively demonstrable at follow-up. Operative data are shown in Table 2. Patients' analgesic requirements were compared with the analgesia given to 12 consecutive patients undergoing colposuspension (average weight 73 kg). The average amount of papaveretum after colposuspension was 52·5 mg which is approximately double the amount required after the Stamey procedure (27·6). The average requirement for oral dihydrocodeine tartrate and paracetamol was the same in both groups.

At 3-month follow-up, 14 patients continued to complain of stress incontinence and 24 of urge incontinence. Objectively 26 patients had genuine stress incontinence and 15 patients had detrusor instability. The six patients with consistent detrusor instability remained incontinent and continued to have detrusor instability when assessed postoperatively. The status of the operator made no difference to the outcome.

Discussion

This study has been terminated owing to the poor results but follow-up will continue for 3 years.

The success rate of the Stamey operation seems to show great variation. Stamey *et al.* (1975) claimed a subjective cure rate of 93% in women with a mean age of 60 years (37–88 years). Mundy (1983) achieved an objective cure rate of 40% for a much younger population than our own, with a mean age of 48 years (29–70 years). Abrams (1988) obtained a subjective and partially objective cure rate of 80% for patients with a mean age of 55 years (17–88 years). All series contained primary and secondary operations

What are the reasons for the poor success rate? Failure due to the ageing process may result from either non-surgical or surgical causes. The former is likely to be the atrophic change of the urothelium, which remains unable to provide a urine-tight seal despite improvement in bladder neck elevation and consequent enhancement of abdominal to urethral pressure transmission. The surgical cause is due to sutures cutting through atrophic fascia. At time of surgery, this occurred when the suture was being tightened. The suture was only reinserted if the bladder neck failed to be elevated by tying the other suture. In this series five patients had sutures that cut through at time of surgery. In three, who remained incontinent, there was failure of bladder neck elevation, whilst the remaining two patients achieved bladder neck elevation and were dry. During follow-up, one patient who had been continent fell, she felt something snap and developed incontinence. Further bladder neck surgery revealed that one suture had broken. Because of the atrophic nature of the tissues in the elderly, we agree with Abrams (1988) that it is important to minimize vaginal dissection around the bladder, to avoid disrupting the pubocervical fascia. In those patients who had another operation after the Stamey procedure failed, invariably the vaginal buffer had migrated from the bladder neck area superiorly towards the rectus sheath. We do not feel that any neurological deterioration associated with ageing is a causative factor; Gillon & Stanton (1984) reported an objective cure rate of 89% at 1 year after colposuspension in a similarly aged population.

Both Mundy (1983) and ourselves locate the bladder neck and insert Stamey sutures from below, because it seems more accurate as the bladder neck can actually be seen at the time of insertion. Passage of sutures from above is a relatively blind procedure. It is difficult to believe that this minor modification is responsible for the differences in our results; it is more likely that these are due, in part, to the fact that Stamey's results are subjective whereas Mundy's and ours are objective.

A further factor resulting in failure could be the end-point of suture tension. The techniques used by Stamey, Abrams, Mundy and ourselves have been devised by the surgeons involved and have not been compared objectively; such assessment is necessary.

The lateral chain cystogram was initially used to provide an objective index of bladder neck position and, possibly, of prognosis. Subsequent review failed to show any difference between continent and incontinent patients.

Is there a suitable procedure for the elderly? The potential advantages of the Stamey procedure are a brief operating time, low operative and postoperative morbidity and low postoperative analgesia requirements. The disadvantages include minimal dissection and consequently poor subsequent fibrosis, and reliance upon two sutures to maintain the bladder neck in an elevated position. Whilst the elderly are likely to be less energetic than younger patients, sudden stress, such as that due to a fall, cannot be avoided, and when combined with the atrophic nature of the tissues may result in failure of long-term effective bladder neck support. The operation might be reserved for the elderly patient with mild pre-operative stress incontinence but, on balance, we would now prefer a procedure such as that described by Raz (1981); although it still relies on only two sutures, these sutures do take a more secure bite of pubocervical tissue and are less likely to cut through. In our experience so far, the operating time, morbidity and postoperative requirements for analgesia are similar.

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The effect of maternal bladder volume on fundal height measurements

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Summary. The effect of maternal bladder volume on fundal height measurements was studied in 200 non-obese Black women between 16 and 42 weeks gestation. Fundal height measurements were obtained by the same examiner immediately before and immediately after each subject voided. Examiners were blinded to fundal height measurements and the amount of urine voided. Prevoid fundal height measurements were significantly larger than postvoid fundal height measurements. The differences between pre- and postvoid fundal height measurements varied from −2·8 to 4·6 cm (mean 0·63 cm, SD 1·26). Postvoid fundal height measurements were smaller than the prevoid measurements in 69·5% of the women, and 34·5% of the differences were > 1·0 cm. Women who had voided within 30 min before measurement had significantly smaller differences between pre- and postvoid fundal height measurements (n=20, mean 0·16, SD 1·22) than women who voided more than 30 min before measurement (n=179, mean 0·68, SD 1·27). These findings indicate that women should be instructed to void within 30 min before fundal height measurements are obtained.

Fundal height measurements can assist clinicians in identifying pregnancy complications such as fetal growth aberrations (Villar & Belizan 1986), multiple gestation (Smibert 1962; Westin 1977), amniotic fluid volume disorders (Westin 1977), hydatidiform mole (Kohorn 1984), and errors in estimating gestational age. The measurements have appeal for clinical use because they are inexpensive, non-invasive, readily available, and acceptable to patients.

Distension of the maternal bladder has long been thought to influence the fundal height measurement (Spiegelberg 1887) and decrease the predictive validity of measurements. However, the effect of urinary bladder fullness on fundal height measurements during pregnancy has not been studied extensively; literature searches located only two studies on this topic. Although both studies demonstrated remarkable differences between the pre- and postvoid fundal height measurements, the studies are limited in their application to routine clinical practice. In the first investigation (Smibert 1962), an unspecified number of the 66 women who participated in the study were instructed to come to the prenatal visit with their bladders '. . . as full as possible' (p. 128). In the second investigation (Worthen & Bustillo 1980), fundal height measurements were obtained from pregnant

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women who had filled their bladders for an ultrasound examination. Thus, the effect of bladder volumes observed under common clinical situations has not been described previously. The purpose of this investigation was to describe the effect of maternal bladder fullness on the fundal height measurement in pregnant women at their routine prenatal visits.

Subjects and methods

Preceding the collection of data, paper tape measures were prepared from laminated, white, unmarked paper. The paper was cut into 20 × 0·5 inch (50·8 × 1·27 cm) strips. Each strip was marked with a line approximately 2·5 cm from the end of the paper. This mark was used as the zero point in the measuring process. Each strip was also marked with the woman's study number and whether the measurement was obtained before or after the woman voided.

After this study was approved by the Institutional Review Board of the University of Illinois at Chicago, a convenience sample of 200 pregnant women was selected from patients registered for prenatal care at the university clinic. Criteria for selection were as follows: prepregnancy body-mass index < 25 (body-mass was calculated as W/H^2, where W is prepregnancy weight in kilograms and H is height in metres) (Robbins & Trowbridge 1984); gestational age between 16 and 42 weeks; Black race; and informed consent to participate in the study.

Women were asked to participate in the study either immediately before or immediately after they were examined by the clinician responsible for their care. After women consented to participate, the following information was obtained from the prenatal record and verified with the woman: prepregnancy weight; present weight; height; gravidity; parity; age; and date of the last normal menstrual period. Gestational age was calculated from the first day of the last normal menstrual period unless a sonographic assessment of gestational age was performed before 27 weeks gestation and the sonographic assessment of gestational age differed by more than 11 days from the dates calculated from the last normal menstrual period.

The prevoid fundal height measurement was obtained with the woman in a supine position on an examining table with her legs extended fully and arms placed at her sides. The blank tape measure was placed in the midline of the maternal abdomen. The uppermost border of the symphysis pubis was identified by palpation and the zero mark of the tape measure was placed on that point and sustained with digital pressure from the fingers of the examiner's right hand. The uppermost border of the uterine fundus was identified by palpation, and the tape measure was brought to that point. The tape measure remained in contact with the skin in the midline of the maternal abdomen for the entire length of the uterus. The point where the blank tape measure intercepted the uppermost border of the uterine fundus was marked with a pen, and then the tape measure was placed in an envelope.

After the prevoid fundal height measurement was obtained, women were asked to estimate their subjective sensation of bladder fullness on a scale of one to five, with one representing no urge to void and five representing a very strong urge to void. Women were then asked to estimate the amount of time that had passed since they had last voided. The examiner estimated maternal bladder fullness by inspecting and palpating the area immediately above the symphysis pubis. Bladder fullness was estimated on a five-point scale, with one representing no distension and five representing gross distension.

Women were then instructed to go to the bathroom and void into a urine collection device that fitted securely into the toilet, and were asked not to place any paper in the device. After voiding, women covered the container with a cloth and handed it to the examiner, who carried it back to the examination room. The examiner obtained the postvoid fundal height measurement using the technique described above and placed the tape measure in the woman's data collection envelope. The urine was transferred into a graduated cylinder and volume was determined to the nearest 2 ml by reading the lower meniscus of the fluid. Urine volume was recorded on the data collection form, the form was placed in the woman s data collection envelope, and the envelope was sealed. All data were collected by two of the authors (K.G.O. and R.V.P.). The pre- and postvoid fundal height measurements for each subject were obtained by the same examiner.

At the completion of data collection all of the paper strips were measured to the nearest millimetre by two of the investigators. If the differences between the two investigators' measurements exceeded 1·0 mm, the measurement was repeated a third time.

Data were analysed using the Statistical Analysis System (SAS, Cary, NC, USA) computer programs. A Type I error of 5% was used for all tests of statistical significance except for tests of homogeneity of variance wherein a Type I error of 1% was used. Two-tailed tests were used for all tests except for comparison of the effect of time on the differences between pre- and postvoid measurements; one-tailed tests were used for these comparisons. Differences between pre- and postvoid fundal height measurements were calculated by subtracting the postvoid from the prevoid measurement.

Results

The obstetric and demographic characteristics of the sample population are described in Table 1.

The differences between pre- and postvoid fundal height measurements varied from −2·8 to 4·6 cm, with a mean of 0·63 cm (SD 1·26) (Table 2). A paired *t*-test demonstrated that prevoid fundal height measurements were significantly larger than the postvoid fundal height measurements (t=7·01, d.f.=199, $P<$ 0·01). Postvoid fundal height measurements were smaller than prevoid measurements in 139 (69·5%) women, and the differences were > 1·0 cm in 69 (34·5%).

Spearman's rank correlation coefficients demonstrated that the differences between pre- and postvoid fundal height measurements were not correlated with the women's estimates of bladder fullness (r_s=0·16), examiners' estimates of bladder fullness by inspection (r_s=0·09), or examiners' estimates of bladder fullness by palpation (r_s=0·04).

Table 1. Anthropometric and obstetric characteristics of 200 subjects

Characteristic	Mean (SD)
Height (cm)	162·10 (6·65)
Prepregnant weight (kg)	55·70 (7·03)
Prepregnant BMI (kg/m^2)	21·19 (2·26)
Present weight (kg)	67·29 (10·18)
Gestational age (weeks)	31·35 (6·22)
Parity	*n* (%)
0	83 (41·5)
1	55 (27·5)
2	28 (14·0)
3	19 (9·5)
4	11 (5·5)
≥5	4 (2·0)

The effects of parity, gestational age, time since last voiding, and examiner on the differences between pre- and postvoid fundal height measurements are described in Table 3. Parity, gestational age, and examiner did not significantly influence the differences between pre- and postvoid fundal height measurements.

Time since last voiding did influence the differences between pre- and postvoid fundal height measurements. Differences between pre- and postvoid measurements were significantly smaller in women who voided within 30 min before fundal height measurements were obtained than those of women who voided more than 30 min before the measurements were obtained. However, differences between the pre- and postvoid fundal height measurements of women who voided within 60 min before fundal height measurements were obtained were not significantly different from those of women who voided more than 60 min before the measurements were obtained. A Pearson's product moment correlation demonstrated that there was not a linear relation between time since last voiding and the differences between pre- and postvoid fundal height measurements (r=0·02, P=0·75).

The amount of urine voided varied between 0 and 354 ml (mean 76·5, SD 54·6). Estimates of the amount of time that had passed since they last voided varied between 15 and 240 min in 199 women (mean 92·2, SD 42·2). Comparison of the amount of urine voided demonstrated that the 20 women who had voided within 30 min of measurement had smaller amounts of urine (mean 48·9 ml, SD 33·8) than the other 179 women who had voided more than 30 min before the measurements (mean 79·8 ml, SD 55·7). A two-sample *t*-test demonstrated that these differences were statistically significant (t=2·42, d.f.=197, P=0·02).

Discussion

The findings of this study support the assumption that fullness of the maternal bladder can affect fundal height measurements. However, this effect was not observed consistently, and the average effect was small. Previous investigators have reported much larger differences than those observed in this study. Worthen & Bustillo (1980) reported that the average decrease in the

Table 2. Differences between pre- and postvoid fundal height measurements

Difference (cm)	*n*	(%)
−3·0 to −2·1	2	(1·0)
−2·0 to −1·1	14	(7·0)
−1·0 to −0·1	32	(16·0)
0	13	(6·5)
0·1 to 1·0	70	(35·0)
1·1 to 2·0	46	(23·0)
2·1 to 3·0	16	(8·0)
3·1 to 4·0	4	(2·0)
4·1 to 5·0	3	(1·5)

fundal height measurement after voiding varied from 2·3 to 3·1 cm, depending on the gestational age. In the present study the mean difference between pre- and postvoid measurements was only 0·63 cm.

There are two plausible explanations for the smaller differences between pre- and postvoid fundal height measurements observed in our study. First, previous investigators studied subjects who had filled their bladders for an ultrasound examination or who were instructed to come to their prenatal visit with their bladders as full as possible. Under normal circumstances, pregnant women usually do not allow their bladders to become distended to the extent required for those two studies. Thus, the pregnant women measured in this study probably had smaller volumes of urine in their bladders than the women who participated in the two previous studies. A larger effect may be observed in other settings where patients are encouraged to consume liberal amounts of fluids while waiting for their prenatal appointment. In the present study, fluids were only available to subjects if they left the clinic waiting room and walked to a water fountain.

The second reason for the smaller differences observed in this study was that there was probably more examiner error in the measurements obtained in this study. In the study reported by Worthen & Bustillo (1980), the landmarks used to obtain fundal height measurements were identified for the examiners; the symphysis pubis was marked and the uterine fundus was identified with ultrasound. In the present study, examiners were instructed to identify the anatomical landmarks used to obtain fundal height measurements using the techniques that they used routinely in clinical practice. The finding that 24% of the postvoid measurements were larger than prevoid measurements may indicate that there was examiner error in obtaining the measurements. Most of these differences were < 1·0 cm, and almost all were within 2·0 cm. Although this amount of error is consistent with the intra-examiner differences reported by previous investigators (Bagger *et al.* 1985; Engstrom 1985), it is possible that other examiners would have less error and, therefore, find a larger effect of bladder volume. Future studies of the effect of bladder volume should be designed to include replicate pre- and postvoid measurements so that the amount of examiner error can be quantified. Studies should also be designed to determine whether examiner error can be reduced, because examiner error can decrease the predictive validity of fundal height measurements.

Although the mean difference between pre- and postvoid fundal height measurements in this study was small, 34·5% of the differences exceeded 1·0 cm. Because clinicians frequently expect the fundal height to grow approximately

Table 3. Effects of parity, gestational age, examiner, and time since last voiding on the differences between pre- and postvoid fundal height measurements

Variable	*n*	Mean (SD)	*t* or *F*	*P* value
Parity				
Nulliparous	83	0·69 (1·27)	0·61*	0·54
Multiparous	117	0·58 (1·26)		
Gestational age (weeks)				
≤20	18	0·46 (0·88)	0·71†	0·61
21–24	14	0·62 (1·45)		
25–28	29	1·00 (0·99)		
29–32	49	0·54 (1·45)		
33–36	48	0·50 (1·12)		
37+	42	0·69 (1·43)		
Examiner				
One	130	0·72 (1·22)	1·48*	0·14
Two	70	0·45 (1·34)		
Last void				
≤30 min	20	0·16 (1·22)	1·73‡	0·09
>30 min	179	0·68 (1·27)		
Last void				
≤60 min	62	0·69 (1·31)	0·44‡	0·66
>60 min	137	0·60 (1·25)		

* *t*-value, two-tailed two-sample *t*-test.
† *F*-value, analysis of variance.
‡ *t*-value, one-tail two-sample test.

1·0 cm/week, fullness of the maternal bladder could cause the clinician to assume incorrectly that adequate uterine growth had occurred. The finding that 11·5% of the differences exceeded 2·0 cm and differences as large as 4·6 cm were observed is worrying, because differences this large could cause the clinician to overlook serious pregnancy complications or intervene unnecessarily in normal pregnancies. Thus, fullness of the maternal bladder could decrease the predictive validity of fundal height measurements.

Women's and examiners' estimates of bladder fullness were not correlated with the differences between pre- and postvoid fundal height measurements. This finding indicates that clinicians should not depend solely on their own or patient's assessments of bladder fullness to determine whether they should instruct women to void before fundal height measurements are obtained.

The amount of time since last voiding may influence the difference between pre- and postvoid measurements. In this study women who had voided within 30 min of measurement had smaller differences than women who voided more than 30 min before the measurements. By 60 min, however, the differences were not statistically or clinically significant. Thus, women should be instructed to void within 30 min of fundal height measurement.

The results of this study are limited to Black women. The effect of maternal bladder volume on fundal height measurements should be studied in other racial groups to be certain that there are not anthropometric differences that either increase or decrease the effect of bladder volume.

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Cystic uterine fibroid: an unusual ultrasonic appearance. Case report

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Case report

A 50-year-old postmenopausal woman was referred for pelvic ultrasonography because of vaginal bleeding. Scanning revealed a large mass in the pelvis. The mass was subdivided by fine septa. In some parts of the mass the contents were echogenic but in other parts the contents were anechoic and clearly cystic with a horizontal level where the echogenic contents had gravitated to the dependent part of the cysts (Fig. 1). On repositioning the patient, the contents of the mass were seen to be liquid and moved freely within the confines of the septa. It was not possible to determine whether the mass arose from the uterus or whether it was closely applied to and indenting the posterior wall of the uterus. Because of its appearance a diagnosis of ovarian tumour was made and the patient underwent laparotomy.

At operation the uterus was found to be enlarged with an external appearance typical of a fibroid uterus. The ovaries were normal and no other abnormalities were discovered within the pelvis. A hysterectomy was therefore performed.

The uterus measured 22 × 16 × 16 cm. On sectioning, a 14 cm cavity containing heavily blood-stained fluid was seen. Fine incomplete septa traversed the cavity. Other areas of the myometrium contained typical-looking fibroids. Microscopically the wall of the cyst consisted of a layer of cellular tissue up to 1 cm thick showing moderate pleomorphism but only infrequent mitoses. There was poor demarcation between the wall and the myometrium but no evidence of invasion. The microscopic appearance of the other more typical-looking fibroids was similar. Immunohistochemistry confirmed the tumour to be of smooth muscle origin and a histological diagnosis of cellular leiomyoma was made.

Discussion

The ultrasonic appearance of uterine fibroids is well described and sufficiently constant to allow a confident diagnosis by clinical examination and ultrasound alone. The appearance depends partly on the size and position of the fibroid but typically there is a deformity of the uterine contour and abnormal texture compared to the normal myometrium. The fibroid is less echogenic unless calcification is present. Difficulties can arise in distinguishing the echo-free appearance of a pedunculated solid homogeneous fibroid from a cyst in the adnexal regions but attention to through-transmission of the beam should overcome this. More serious difficulties arise if degeneration has occurred within the fibroids. Degeneration results in the replacement of the solid stroma by, usually, mucinous material. As this occurs, more interfaces result and the fibroid becomes progressively echogenic (Sarti 1987). This may raise a differential diagnosis of uterine cancer or hydatidiform mole (Rinehart *et al.* 1981).

The ultrasonic findings in this mass suggested an ovarian origin. Cystic masses are usually associated with benign and malignant ovarian tumours or with disease of the fallopian tubes and are only rarely associated with uterine tumours. The finding of fluid levels within this cystic mass strongly suggested a diagnosis of pelvic dermoid as such an appearance is well described and relatively characteristic (Sarti 1987).

A uterine fibroid with a similar ultrasonic appearance to the case described here was

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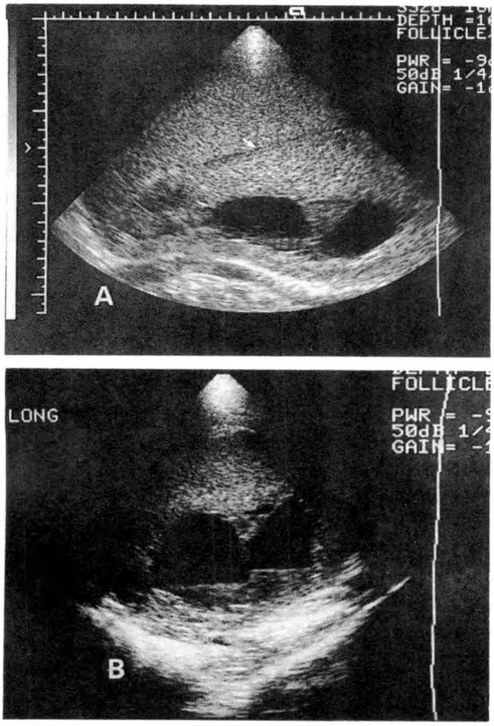

Fig. 1. Real-time ultrasound scan of pelvic mass demonstrating (A) fine septum (arrowed) traversing echogenic fluid and (B) fluid levels within the mass.

described by Togashi *et al.* (1986). However, fluid levels were not present and the contents of the cyst were mucinous. On the basis of ultrasonic and CT appearance this was diagnosed as a malignant ovarian tumour. Maenpaa *et al.* (1987) also made a diagnosis of ovarian cancer in a case of uterine leiomyoma with mucin-containing cysts because of the ultrasonic and CT appearance. In this case, however, the cysts were less well defined and again showed no internal levels. A well-defined multiloculated cyst in a degenerated leiomyoma was described by Delarue *et al.* (1987). The loculi had haemorrhagic or clear contents. Here also levels were not described and a diagnosis of ovarian cyst was made initially on ultrasonic appearance.

A report of two cases of cystic parametrial fibroids (Nocera *et al.* 1984) included a description of debris forming a level in the dependent parts of the cysts in one of the cases. The histology of the fibroid showed necrosis and liquefaction in the deeper parts resulting in the pattern of cystic degeneration. Both cases were initially diagnosed as ovarian cystadenoma.

In our patient there was no histological evidence of degeneration, and the extremely haemorrhagic contents suggested recent haemorrhage into a fibroid. The levels within the cysts were presumably due to cellular debris. Although the fibroids were not histologically typical because of their increased cellularity, solid fibroids with an identical histological appearance were also present within the uterus, and the unusual ultrasonic features are considered by the authors to be due to haemorrhage into a fibroid.

Differentiation of uterus from adnexal structures may sometimes be difficult on ultrasound examination especially if the uterus is enlarged and the adnexal structures are displaced. Some of these difficulties can be overcome by the use of the transvaginal scanning technique. Although a cystic appearance on ultrasound examination is unusual in diseases of the uterus the occurrence of cystic fibroids should be borne in mind.

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Needle aspiration of simple ovarian cysts in pregnancy. Case reports

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Case reports

Patient no. 1

A 30-year-old primigravida presented in the casualty department at 9 weeks gestation complaining of pain in the right iliac fossa. Symptoms resolved spontaneously. On booking at the antenatal clinic 2 weeks later she was found to have an ovarian cyst. Ultrasound confirmed a viable fetus at 11 weeks gestation and a smooth-walled 9 × 5 × 7 cm right-sided ovarian cyst occupying the right iliac fossa. She was admitted and the cyst was aspirated transabdominally using local anaesthesia and ultrasound control, 220 ml of straw-coloured fluid being obtained. Cytological examination demonstrated luteinized granulosa cells with no evidence of malignancy. The pregnancy continued uneventfully. Ultrasound examination at 34 weeks gestation showed no evidence of an ovarian cyst. Labour began spontaneously at 41 weeks. A healthy female infant weighing 2800 g was born vaginally. Apgar scores were 8 at 1 min and 10 at 5 min. Breast-feeding was established and the puerperium was uneventful. Six weeks after delivery, ultrasound revealed no pelvic abnormalities.

Patient no. 2

A 30-year-old primigravida booked at the antenatal clinic at 13 weeks gestation. Routine ultrasonography confirmed dates and revealed an 8 × 7 × 6 cm simple ovarian cyst to the right and posterior to the uterus. She was admitted at 17 weeks gestation and the cyst was aspirated transvaginally under general anaesthesia and ultrasound control. A 150-ml volume of clear fluid was withdrawn and cytology was benign. The scan was repeated at 30 weeks gestation. Good fetal growth was noted and there was no evidence of repeat accumulation of the cyst. Labour was induced at 42 weeks. A healthy female infant was born by Kiellands forceps with a birthweight of 3920 g and Apgar scores of 9 and 10 at 1 and 5 min respectively. Breast-feeding was begun. A pelvic ultrasound scan at 6 weeks after delivery showed a 4 × 2 × 4 cm right-sided ovarian cyst. The scan was repeated 3 months later and no abnormalities were seen.

Patient no. 3

A 40-year-old woman booked at the antenatal clinic at 14 weeks gestation. She had previously been delivered of a healthy male infant by emergency caesarean section for cephalopelvic disproportion. Her subsequent pregnancy was complicated by a hydatidiform mole. Routine ultrasonography revealed a 7 × 5 × 6 cm simple ovarian cyst on the right side. The cyst was aspirated transabdominally with local anaesthesia and ultrasound control. A 50-ml volume of fluid was obtained and on cytological examination benign cells only were seen. The pregnancy was otherwise uncomplicated and at 38 weeks she was delivered by elective caesarean section. A healthy female infant was born in excellent condition with a birthweight of 3160 g. Inspection of the ovaries at the time of operation revealed a 3 × 3 × 4 cm left-sided ovarian cyst which was aspirated. Cytology was benign. The puerperium was uncomplicated and the infant was breast-fed. The patient was subsequently lost to follow-up.

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Patient no. 4

A 28-year-old multipara was found to have a right-sided 16 × 11 × 9 cm simple ovarian cyst at routine ultrasonography at 18 weeks gestation. Transabdominal aspiration under ultrasound control and local anaesthesia yielded 1500 ml of straw-coloured fluid. Cytology was benign. The pregnancy proceeded uneventfully. At 35 weeks gestation the cyst had accumulated again. Labour started at 39 weeks and a healthy 3700 g male infant was born spontaneously with Apgar scores of 3 at 1 min and 8 at 5 min. Breast-feeding was started. Six weeks after delivery ultrasonography confirmed the presence of a 10 × 9 × 15 cm ovarian cyst. At laparotomy a large cyst was found arising from the right ovary. Salpingo-oophorectomy was performed. Histology revealed a serous cystadenoma.

Discussion

Management of ovarian cysts in pregnancy remains controversial. In our series all patients were found to have smooth-walled unilateral cysts with no internal echoes. Three women were asymptomatic while the other had experienced episodes of acute abdominal pain. The cysts were managed by needle aspiration and the approach used was determined by the accessibility of the cyst. In patients 1, 3 and 4 the cysts were aspirated transabdominally. This procedure was performed on the antenatal ward and patients were fully informed beforehand. Two operators are required; the first performs a scan to confirm fetal viability and locate the cyst. Dimensions of the cyst are noted. The second operator infiltrates the anterior abdominal wall with 1% lignocaine. The cyst is punctured under ultrasound control and aspirated with a 20-gauge spinal needle. Aseptic technique is used. The fetal heart is checked at the end of the procedure. Patients are observed for a few hours and then allowed to go home. The transabdominal approach was well tolerated by all patients and the duration of the procedure ranged between 20 and 45 min.

In patient 2 a transvaginal approach was used as the cyst was located in the pouch of Douglas.

There were no cyst-related complications in these pregnancies after aspiration.

Ovarian cysts are readily detected during pregnancy with routine pelvic examination at booking and ultrasound scanning. Hogston & Lilford (1986) reported the prevalence of cysts detected by ultrasound in the first half of pregnancy to be 1 in 190.

Surgical removal of ovarian cysts has been advocated in the second trimester because of the risk of complications. Elective surgery is recommended as this is accompanied by fewer fetal and maternal complications than emergency laparotomy (Hess *et al.* 1988). Torsion, rupture or haemorrhage into the cyst may occur during pregnancy or the puerperium. Later in pregnancy, ovarian tumours may cause malpresentation and lead to obstructed labour but this is uncommon. Malignant ovarian disease in pregnancy is rare and estimates of its incidence vary between 1 in 18 000 pregnancies (Munnell 1963) and 1 in 25 000 (Chung & Birnbaum 1973). In the presence of an ovarian tumour, malignancy is found in up to 8·0% of patients (White 1973) depending which series is considered.

However, abdominal surgery involves both maternal and fetal risks. Anaesthesia remains an important cause of maternal mortality (Report on Confidential Enquiries into Maternal Deaths 1979–1981) and should be avoided in pregnancy when possible. Immobility during the immediate postoperative period increases the risks of thromboembolic disease. Fetal loss rates after ovarian cystectomy have been variously quoted as between 18 and 25% (Gustafson *et al.* 1954; White 1973; Hill *et al.* 1975). Needle aspiration provides an alternative approach to management of ovarian cysts in pregnancy. In our limited series the safety of this method for both mother and fetus is encouraging.

Transabdominal aspiration is well tolerated when local anaesthesia is used (de Crespigny *et al.* 1985). Needle tract metastases from an unsuspected malignancy are rare (Livraghi *et al.* 1983). This approach is not appropriate if malignancy is suspected. Ultrasound characteristics permit correct diagnosis of benign and malignant ovarian neoplasms in over 90% of patients (Meire *et al.* 1978). The cyst fluid should always be investigated cytologically.

We suggest that needle aspiration under ultrasound control provides a safe alternative to laparotomy when an ovarian cyst is detected in pregnancy. This approach is appropriate for cysts >5 cm in diameter which are unilocular and smooth walled with no internal structure. Cysts >10 cm in diameter should be removed surgically as they are likely to accumulate again. Patients should be selected carefully for this procedure and those with a history of previous pelvic surgery, endometriosis or pelvic inflammatory disease may be unsuitable. Transvaginal aspiration should be performed only by an experienced operator.

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Darier's disease localized to the vulva. Case report

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Case report

A 43-year-old housewife of European ethnic origin, mother of two children, was seen in the gynaecological clinic having had irregular periods and pruritus vulvae for 1 year. The pruritus was especially bad at night and aggravated by coitus. In the past she had had a penicillin-associated skin reaction and had tended to develop localized rashes with topical antiseptics, elastoplast and certain metals. She was not using any regular medication and did not smoke or drink alcohol. No one in the family had skin disease and the household did not include any pets.

She was of average weight for height and her skin looked normal. Except for a small urethrocoele, the vulva and vagina appeared normal with no discharge: a high vaginal swab yielded no growth. The cervix was healthy with normal cytology and the uterus was axial, mobile and slightly bulky.

Eight weeks later she was admitted for diagnostic curettage and vulval biopsy. Four biopsies were taken randomly from the labia majora and perineum. Macroscopically normal endometrial tissue was reported as proliferative and consistent with anovulatory cycles. Histological examination of the perineal skin biopsies showed mild hyperplasia but the labial biopsies revealed acanthosis and hyperkeratosis with suprabasal clefts, corps ronds in both the prickle cell and granular layers and grains in the keratin layer (Fig. 1). These findings are compatible either with Darier's disease or benign familial pemphigus. The features of these two conditions are compared in Table 1 from which it would appear that the findings in our patient are more in keeping with Darier's disease. The vulva was treated with a mild corticosteroid cream and the pruritus had settled completely when she was reviewed 3 months later. At that time she had no dermatological complaints nor were any skin lesions detected on a careful search of the whole body.

Discussion

Darier's disease, also known as keratosis follicularis, has two main variants. The generalized form is more common and is autosomal dominant whilst the other less usual form is localized and non-hereditary. The lesions in the generalized disease are characteristically dirty, warty papular excrescences, usually coalesced into symmetrical patches on the face, trunk and flexural aspects of the extremities. The vulva is commonly affected in this form with pigmented hyperkeratotic papules developing after puberty. The typical picture in the localized non-hereditary version is an acneiform pattern of keratotic papules in a zostiform arrangement which is usually limited to just one part of the body (Ackerman 1972; Kawaguchi *et al.* 1982; Ueda *et al.* 1983). The skin lesions in the two forms are almost identical histologically with suprabasal acantholysis, corps ronds, nuclear grains and dyskeratosis as the definitive features (Friedrich & Wilkinson 1982, Domonkos *et al.* 1982).

In an exhaustive review of the literature, Kinbara *et al.* (1976) found no case of Darier's disease localized to the vulva. The usual sites involved were abdomen, back and waist. Most patients were female (21 out of 36) and >20

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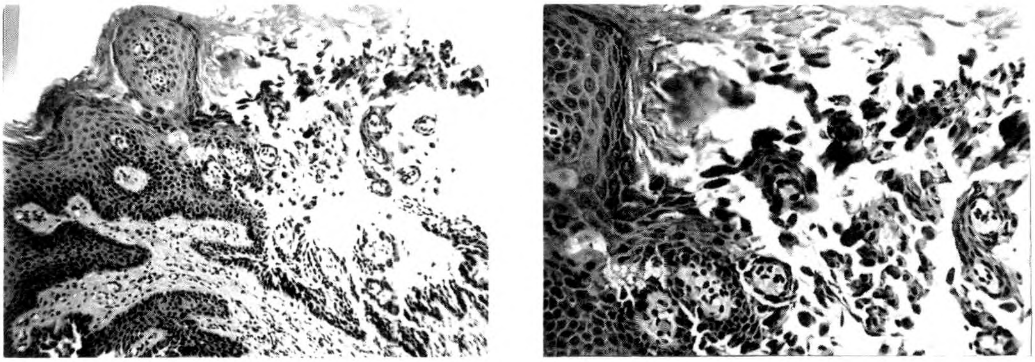

Fig. 1. Photomicrograph of the vulval biopsy illustrating the typical acanthotic hyperkeratotic squamous epithelium with acantholysis, corps ronds and nuclear grains.

years of age at the time of diagnosis. Pruritus was the usual presenting symptom. To our knowledge there is no report of a case without visible lesions, but transient forms of the disease have been described (Ackerman 1972; Domonkos *et al.* 1982) and may account for the lack of overt pathology in our patient. Therapy for the localized form is the topical use of a corticosteroid or aromatic retinoid cream (Domonkos *et al.* 1982). Tar-, salycylate- and sulphur-containing ointments may also be helpful.

Darier's disease must be distinguished from benign familial pemphigus (BFP), a condition characterized by persistent recurrent bullous and vesicular dermatitis, usually on the sides of the neck, axillae and flexures (Table 1). The primary lesion of BFP is a bulla or vesicle on seemingly normal skin (Domonkos *et al.* 1982), and cases confined to the vulva have been reported (Ridley 1975). Our patient had no family history of a similar condition, nor had she the typical vesicles or bullae seen in BFP, and the histological appearances were more in keeping with Darier's disease (Table 1), the only one of the two in which an evanescent form has been described.

Our patient illustrates two important points. First, the vulva, although often regarded as a special structure, is prone to the same skin diseases as the rest of the integument. Second, vulval biopsy may still be of value even in the absence of visible skin abnormality (Jeffcoate 1975). A vulval biopsy can be obtained under local anaesthetic as an outpatient and, if employed in all cases of vulval pruritus, may lead to earlier diagnosis of premalignant conditions and reveal interesting and treatable rarities as on this occasion.

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Table 1. Characteristic features of Darier's disease compared with benign familial pemphigus

	Darier's disease	Benign familial pemphigus
Family history	Autosomal dominant in generalized form only	Autosomal dominant, no family history in 33%*
Evanescent form	Yes	No
Macroscopic	Typically crusted hyperkeratotic papules	Vesicles/bullae are characteristic
Microscopic	Small suprabasal lacunae	Large suprabasal bullae
	Corps ronds common in prickle and granular layer	Corps ronds rare, only seen in granular layer
	Nuclear grains in keratin layer	Epidermal layers widely separated
	Dyskeratosis common	Dyskeratosis rare

* Domonkos *et al.* (1982).

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Endometrioid carcinoma of the ovary: an unusual cause of postpartum collapse. Case report

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Case report

This 28-year-old primigravida booked at 11 weeks gestation and subsequently attended clinic regularly. She had certain dates and the uterine size was equivalent to the period of gestation throughout the pregnancy. The antenatal course was uneventful.

She was admitted in advanced labour at 37 weeks gestation, and only 15 min after admission progressed to a spontaneous vaginal delivery of a live female infant weighing 2910 g with Apgar scores of 10 and 10 at 1 and 5 min. Intramuscular ergometrine, 0·5 mg, was administered and the third stage was uncomplicated. Whilst the episiotomy was being sutured she vomited once, undigested food only with no haematemesis.

On completion of the episiotomy repair, 20 min after delivery, the patient was found to be unconscious though rouseable. She complained only of epigastric pain. On examination she was pale, sweating and had cold extremities. Her pulse was 120 beats/min and her blood pressure 80/40 mmHg. Examination of the chest was normal. The abdomen was uniformly distended but no guarding or rebound tenderness could be elicited. There was no fluid thrill or shifting dullness, and bowel sounds were absent.

Vaginal examination showed the vaginal blood loss to be minimal and no tear was present in the cervix or vagina. The uterus was well contracted. Rectal examination was normal.

Resuscitation was commenced and an emergency laparotomy performed.

Operative procedure

The abdomen was opened through a midline subumbilical incision. On opening the peritoneum, 1200 ml organized clot and 1700 ml fresh blood were removed. A large flaccid ovarian tumour measuring 30×30×50 cm occupied the abdomen. The tumour contained some solid areas but the capsule was smooth and there was no surface growth. A small area had ruptured, tearing a blood vessel which was actively bleeding, but the capsule of the tumour was intact. The right ovary and tube were normal. The liver, spleen, stomach and bowel were grossly normal. No para-aortic lymph nodes were palpable.

Two litres of blood-stained fluid were aspirated from the tumour before it could be extracted through the abdominal wound and a left salpingo-oophorectomy was performed. Peritoneal lavage was performed.

The patient made an uneventful postoperative recovery subsequent to receiving 5 units of blood. Her haemoglobin on discharge from hospital was 9·5 g/dl.

Pathological examination

The ovarian mass (after aspiration of fluid in theatre) measured 22×23×10 cm. The mass was encapsulated and had a smooth outer surface. The tumour was partly cystic and partly solid with a lot of necrotic tumour tissue. Histological examination showed a complex papillary tumour lined by tall columnar epithelial cells with eosinophilic cytoplasm. The capsule was intact although the tumour had invaded very

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close to its serosal surface. A diagnosis of endometrioid carcinoma of the ovary grade I was made.

The cytology of the aspirated cystic fluid showed clusters of carcinoma cells with hyperchromatic and irregular nuclei. The cytology of the peritoneal washings after evacuation of blood was negative.

The rupture of the ovarian capsule leading to haemoperitoneum led to a clinical staging of stage Ia (ii). A plan was made to treat the patient with 12 courses of oral melphalan, 0·2 mg/kg body-weight. At follow-up after five courses of treatment the patient was asymptomatic and pelvic examination was normal.

Discussion

Endometrioid carcinoma associated with pregnancy is a rare occurrence. To the best of our knowledge, this case represents the third report and the eighth reported case in the English literature, six other cases having been reported by Novak *et al.* (1975) in their paper on 100 cases of ovarian tumours in pregnancy and one by Sommers *et al.* (1985).

The prevalence of ovarian cysts in pregnancy (if confirmed by laparotomy) is 0·2%–0·1% (Ballard 1984). Reports suggest that about 3% of ovarian cysts in pregnancy are malignant but that the prognosis is relatively good (Jubbe 1963; Creasman *et al.* 1971). The good prognosis may be due to earlier diagnosis at antenatal screening or because a more favourable pathological type of malignancy is encountered in pregnant women. Prognosis of endometrioid carcinoma in the non-pregnant patient is most influenced by histological grading and extent of the tumour. Stage I lesions have a 5-year survival of 95·5%, whereas the 5-year survival of stages II–IV is significantly lower: stage II 28%, stage III 4%, and stage IV 0% (Czernobilsky *et al.* 1970). Previous reports suggest that pregnancy does not influence the course of carcinoma of the ovary.

The available information on the management of endometrioid carcinoma in pregnancy is limited. Sommers *et al.* (1985) suggest that treatment by total hysterectomy and bilateral salpingo-oophorectomy appears to be satisfactory for stage I disease. In the series of ovarian carcinoma in pregnancy described by Jubbe (1963) it was suggested that in the older patient who has completed her family, total hysterectomy and bilateral salpingo-oophorectomy is the procedure of choice, but in the younger patient desiring further children a unilateral oophorectomy, when the lesion is unilateral, mobile and confined within an intact capsule, gives a relatively good prognosis and further pelvic operations do not improve the maternal outcome. But adequate follow-up of the patients must be ensured if conservative treatment is used since 20–40% of ovarian carcinomas are bilateral although the second ovary may not be involved for 5–10 years.

The presentation of ovarian carcinoma in pregnancy is extremely variable. Most of the 100 women described by Novak *et al.* (1975) were asymptomatic; only 5% had any evidence of an acute process such as torsion of the pedicle or haemorrhage. In the 26 women described by Jubbe (1963) the most frequent symptoms were painless enlargement of the abdomen (10 women) and lower abdominal discomfort (10 women); only 5% of the women presented with acute intra-abdominal emergencies due to complications of the ovarian tumour.

The widespread use of routine ultrasound in the management of pregnant patients may led to the detection of many ovarian cysts which would have previously passed unrecognized. It has been recommended that all persistent ovarian cysts in pregnancy would require a laparotomy in the second trimester (Dewhurst 1986). Hogston & Lilford (1986) showed that this advice may not be applicable to the asymptomatic cysts discovered by routine ultrasound since most are functional and will disappear spontaneously. Methods are therefore required to distinguish functional from pathological cysts pre-operatively. Goswamy *et al.* (1984) concluded that the ultrasound criteria of malignancy are not sufficiently sensitive to differentiate benign from malignant cysts. Thornton & Wells (1987) in a review of 131 cases of pregnancy complicated by ovarian cysts concluded that conservative management of selected ovarian cysts in pregnancy may be appropriate. They suggest removal of all cysts suspected of torsion or rupture and of those over 10 cm in diameter. All other cysts less than 5 cm in diameter can be managed conservatively. Cysts between 5 and 10 cm in diameter can also be managed conservatively unless they contain septae or nodules or are solid, when they are unlikely to resolve and should be removed.

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SHORT COMMUNICATIONS

A two-dimensional self-retaining vaginal retractor for high obstetric trauma

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Injury to the upper vagina, vault and cervix following delivery can be difficult to deal with because of bleeding and poor access, particularly in obese women. Several assistants are often needed using single-blade side-wall retractors to expose the injured area for surgical repair. A two-dimensional retractor which is effective, easy to use, allows one-man operation and is inexpensive to produce is described with illustrative case reports.

Background and description

Although several devices have been used to deal with this situation, we could only discover one 'purpose-built' instrument—the Dunn's vaginal speculum (Down Brothers and Mayer & Phelps Ltd, Museum). This device is probably rather difficult to introduce because of its fixed diameter and limited depth of penetration (Fig. 1).

The O'Sullivan–O'Connor speculum (Fig. 2) is a four-bladed device, but the anterior/posterior blades are very small and allow intrusion of the vaginal wall into the operative field. Although the lateral blades are adjustable, the sliding sections make the device somewhat unwieldy and oblique angulation (for example to examine the lateral fornix) difficult. Moreover, such a relatively complex design means increased production costs.

The current retractor consists of four straight blades, curved in cross-section, each of which has a locating pin at the outer aspect of the operator end. The retaining ring has four holes drilled at equidistant points so that the four blades can be locked into position to form a tapered cage within the vagina. Operative procedures are then carried out by means of long-reach surgical instruments through the aperture of the locking ring (Figs 3 and 4).

Insertion is effected by holding the two lateral blades 'collapsed' together until the distal ends of the blades are in the lateral fornices. One lateral blade is then fixed to the ring by means of its locating pin, then the other lateral blade is locked to the ring by gently levering the blades apart using the locating pin of the second blade resting on one of the locating holes in the retaining ring as a fulcrum. The anterior blade is then inserted between the retaining ring (which is now suspended at the perineum) and the symphysis, and the locating pin of this blade similarly locked into the ring. The posterior blade is inserted and locked in a similar manner.

The device can either be used with all four blades *in situ,* or only three to provide greater access to any quadrant of the vaginal wall.

The instrument has been made in three sizes: the aperture diameter measuring 60, 70 or 80 mm and the corresponding blade length measuring 100, 120 or 150 mm respectively. All components are made from surgical quality stainless steel.

Case reports

Patient 1

A 28-year-old primigravida weighing 104 kg had an uneventful first stage of labour. Delay occurred in the second stage. The cervix was fully dilated with the fetal head 2 cm below the spines and the position was right occipitolateral. A Kjellands forceps rotation and delivery was performed without apparent difficulty. A second degree episiotomy with a 7 cm vaginal tear was repaired in layers, and no other abnormality was detected. A 4·1-kg boy was born in good condition.

One hour after delivery the lochia was very heavy and the patient showed signs of shock. The uterus was well contracted, but examination under anaesthesia revealed a 'bucket-handle' tear of the posterior cervix from 3 o'clock to 7 o'clock. Because she was very obese, it proved impossible to gain adequate exposure of the

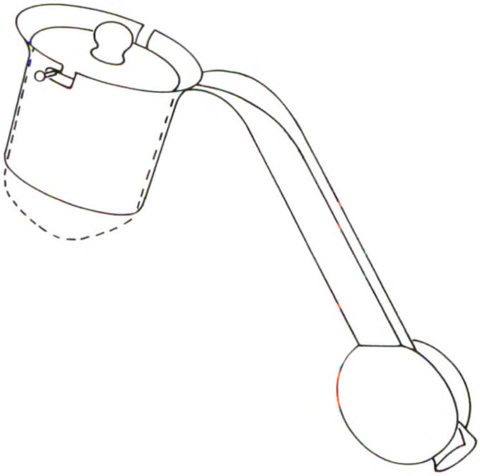

Fig. 1. Dunn's vaginal speculum.

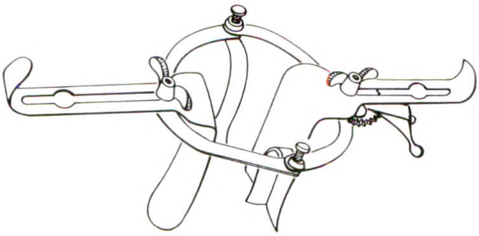

Fig. 2. O'Sullivan–O'Connor vaginal speculum.

vault and cervix using conventional specula. By using the large-sized two-dimensional device, a good view of the cervix was obtained, and it became possible to close the defect using long 'double-jointed' needle holders and toothed dissecting forceps. At follow-up the cervix looked distorted but otherwise had healed well and she was asymptomatic.

Patient 2

This was a 34-year-old parous woman whose first two babies had been born occipitoposterior. Labour at term was uneventful until delay occurred in the second stage of labour due to a persistent occipitoposterior position. A Simpson's forceps delivery was carried out. The baby was born occipitoposterior, and a large third-degree tear involving the distal 80 mm of rectal mucosa resulted. The baby weighed 3·8 kg and was in good condition. By using the small-sized two-dimensional retractor and omitting the posterior blade, an excellent view of the defect was obtained allowing closure in layers, even at the proximal section. The rectum and vagina were soundly healed and the patient was asymptomatic at follow-up.

Conclusion

In the type of situation described, this instrument can prove extremely useful, and we feel has saved at least one patient from an obstetric hysterectomy. The author has now used it on over 20 patients with success. We feel that it can make a valuable contribution in the management of this difficult surgical emergency. Because the design is simple, low cost is a further advantage.

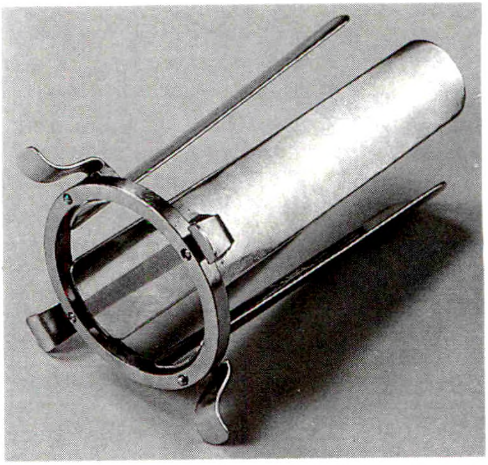

Fig. 3. Assembled two-dimensional vaginal retractor.

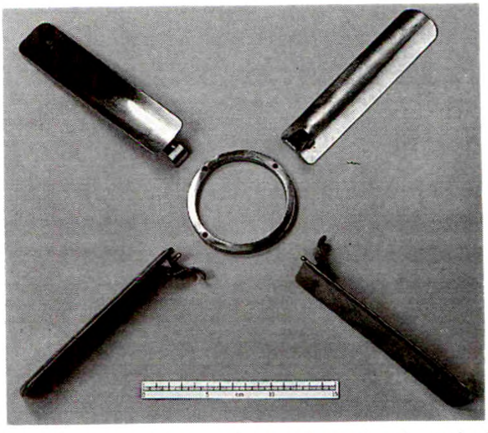

Fig. 4. Components of two-dimensional vaginal retractor.

Acknowledgments

My thanks to Rocket of London Ltd, particularly Colin Atkins, Technical Director, for their help in the development and production of prototypes of this instrument.

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Is it time to review antenatal screening for syphilis?

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Records at the Department of Genitourinary Medicine, Royal Liverpool Hospital, were checked for cases of early syphilis. Records at the Mersey Regional Blood Transfusion Centre were checked for positive serological tests for syphilis and the patients' details were obtained from their maternity hospital and genitourinary medicine clinic notes

The number of women with early syphilis diagnosed at the Department of Genitourinary Medicine, Royal Liverpool Hospital, in the 6-year period 1976 to 1981 was 79, whereas only 18 were diagnosed in the following 6-year period to 1987. Since 1981 there have been six children under two years of age with congenital syphilis reported to the Department of Health and Social Security from the Mersey Region.

A total of 68 786 births occurred between October 1981 and September 1987 at three major maternity hospitals on Merseyside: Liverpool Maternity, Mill Road Maternity and Fazakerley Maternity. The screening test used was the automated Reagin Test or the Venereal Disease Research Laboratory (VDRL) test, and if found positive, further specific tests for syphilis were done.

Ten pregnant women were found to have serological tests for syphilis consistent with treponemal infection at some time. They were predominantly young, unemployed single women; seven were aged 23 or younger, eight were unemployed, seven were single, two were married and one was separated. Three had been previously diagnosed and treated for syphilis and seven were newly diagnosed; however, three of these seven were considered to have a late latent infection (asymptomatic syphilis of at least 2 years' duration) and were thus at low risk of transmission of infection to their fetuses (Adler 1984). One woman had early latent syphilis (asymptomatic syphilis within the first 2 years of infection); she was treated and had a stillbirth at 34 weeks, but autopsy showed no evidence of congenital syphilis. Three women had early latent infection, they were treated and gave birth to healthy babies.

There were 19 biological false-positive results Thus in a total of 68 786 pregnancies investigated, four pregnant women were detected who were at significant risk of transmitting syphilis to their fetuses

Comment

Serological tests for syphilis have been a traditional part of antenatal screening for the prevention of congenital syphilis in Britain since the 1950s (Morton & Harris 1975). In view of the decreasing incidence of early syphilis in women in our clinics in Liverpool, the value of the current syphilis screening policy of a single serological test for syphilis at first antenatal visit was investigated.

Screening tests are clearly valuable when disease prevalence is high, but when prevalence is low, factors such as the timing of the test in pregnancy become important. Ewing *et al.* (1985) searched for examples of congenital syphilis in the Mersey Region from 1975 to 1984 and found seven, but of these only two were discovered by antenatal screening. The other five had negative tests in the antenatal clinic at their booking visit (one was negative as late as 32 weeks gestation), but went on to contract syphilis later in pregnancy. These women were only investigated after a diagnosis of congenital syphilis had been made in their babies, so that more cases were detected postnatally by astute paediatricians than were prevented by the massive antenatal screening programme. Also, these infections were only detected because the infants were symptomatic—it is likely that there were asymptomatic infants who remained undiagnosed.

Estimates of the cost of testing, if performed on the sample of blood taken for other routine tests, excluding cost of needle and syringe, vary from £6.00 (Public Health Laboratory Service private test) to £0.60 per patient (Williams 1985).

If screening for this uncommon disease is considered relevant in modern obstetric practice, it should be performed in such a way that the majority rather than the minority of cases are detected. Selective testing of high-risk groups is not a practical option at overcrowded, busy antenatal clinics. To be effective, allowing for the incubation period, the test should be performed in early pregnancy, in late pregnancy and again postnatally.

Has the time come to reassess the benefit from antenatal screening throughout Britain and to make a decision either to increase the number of tests to the level outlined above or to abandon the present ineffective screening policy?

Acknowledgments

We would like to thank Dr R. Hussey, Dr O. P. Arya and M. Bromilow for assistance, and Mr M. Johnstone, Mrs W. Francis and Mr R. Atlay for access to patient records.

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CORRESPONDENCE

The role of postoperative alkylating agent therapy in early-stage epithelial ovarian cancer

Dear Sir,

We read with interest but also with disquiet the article by Mackintosh *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 353–357]. We recognize that patients referred from non-specialist centres often have primary surgery performed by surgeons without gynaecological oncology expertise. It is, nevertheless, disappointing that in this contemporary series of 'early ovarian cancer' patients, optimal primary surgery was performed in only 15%. This initial shortcoming is compounded by the absence of surgical restaging at the referral centre.

As most patients in this study had suboptimal staging, any comments on the influence of FIGO stage on prognosis and treatment must be viewed with extreme caution. Despite this, the survival of patients with 'stage Ia–b' and those with 'stage Ic, IIa–c' is sufficiently different to suggest that the two groups have different biological behaviour. In neither group, however, is adjuvant therapy of proven benefit. As the authors acknowledge, other trials show excellent long-term survival in patients with stage Ia–b ovarian cancer treated with adequate surgery alone and therefore adjuvant therapy may well not be indicated. For the more advanced group many types of adjuvant therapy have been used. The West Midlands Adjuvant Study comprised 44 patients with histologically confirmed epithelial ovarian cancer (which was centrally reviewed) who had undergone optimum surgical staging and had no macroscopic residual disease; 22 patients had FIGO stage III disease, 16 stage II, and six patients had stage Ic disease. Patients were randomized to receive either high-dose cisplatinum (100 mg/m^2×5) or moving strip whole abdomen radiotherapy according to the Toronto protocol (Dembo *et al.* 1979). There was no significant difference in survival between these two groups ($\chi^2_1 = 2{\cdot}27$, $P = 0{\cdot}13$), and the median survival for the group as a whole was 47 months. This study and those of Mackintosh *et al.* (1989) and Klassen *et al.* (1988) show similar results with a range of adjuvant therapies. This may suggest that all therapies are equally effective, but an alternative, and more likely hypothesis, is that relapse is inevitable in this more advanced group and is not influenced by adjuvant therapy.

It is vitally important, before committing all such patients to potentially toxic adjuvant therapy, that the role of such therapy is tested in a prospective randomized trial against a no-treatment group. Adequate staging must be an essential part of any such study and survival benefits must be weighed against the toxicity of treatment administered to many patients for whom it is unnecessary. A study to answer this question has recently started in the West Midlands but of necessity must be multicentre and will depend on national support to recruit adequate numbers. We would emphasize that adjuvant therapy for ovarian carcinoma remains of no proven benefit and would urge all those concerned with the management of this group of patients to participate in this study.

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Mackintosh J., Buckley C. H., Tindall V. R., Lind M J, Anderson H. & Crowther D (1989) The role of postoperative alkylating agent therapy in early-stage epithelial ovarian cancer. *Br J Obstet Gynaecol* **96,** 353-357.

Authors' reply

Dear Sir,

The letter from Finn and his colleagues expresses disquiet over the low rate of optimal initial surgical resection in patients with ovarian cancer within the North Western region. We share these worries and have taken steps to improve this. Our optimal resection rate has improved over the past few years. However, we disagree that immediate second-look surgery is required for most patients after an initial suboptimal procedure. The majority (80%) had bilateral salpingo-oophorectomy with hysterectomy and had macroscopic evidence of residual tumour. There is no evidence that submitting these patients to a further laparotomy with omentectomy to detect possible microscopic disease is in their best interests (Heintz 1988).

Patients with FIGO stage Ia–b were selected for high-risk features before being treated with adjuvant single aklylating agent therapy. The actuarial relapse-free survival was 89% for this group of patients and is not significantly different from other series not given adjuvant therapy. The results for FIGO stage Ic and II were poor with a relapse-free survival of only 24%. We agree that this represents a high incidence of undetected microscopic disease, but the use of adjuvant cyclophosphamide was a failure and we submit that this approach to adjuvant therapy has little chance of any future success and should not be used. Whether other forms of improved chemotherapy can be used successfully in an adjuvant setting remains the subject of randomized study in a number of centres. Clearly the selection of therapy giving the best chance of success as an adjuvant will be important. Whether adjuvant treatment influences survival in patients with stage Ic, II or III disease with no macroscopic residuum has not been studied in a controlled trial. Neither the West Midlands Adjuvant Study nor that by Klassen *et al.* (1988) had a control group without adjuvant therapy.

The numbers entered into such randomized trials must be sufficient to provide an answer. Small randomized studies are more likely to mislead than help. Finn and his colleagues mention a randomized West Midlands Adjuvant Study comparing two controversial adjuvant approaches which involved only 17 high-risk stage I/II patients. The fact that there was no difference between the radiotherapy and cisplatin arms in this small series does not help answer the controversial question of whether adjuvant therapy has any value compared with controls receiving no adjuvant therapy.

We agree entirely that an important way forward is to select the best available adjuvant therapy and test this in a large controlled randomized trial.

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Heintz A. P. M. (1988) Surgery in advanced ovarian carcinoma: is there proof to show the benefit? *Eur J Surg Oncol* **14,** 91-99.

Secular trend in the rate of small-for-gestational-age infants: Haguenau Study 1971–1985

Dear Sir,

I have read the article by Meyer *et al.* [*Br J Obstet Gynaecol* (1988) **95,** 1257–1263] and I would like to comment on its general approach and statistical methodology. The authors computed smoothed standards for the 10th and 5th centiles, which they used later to measure how many newborns were actually included in the calculated standard for each 3-year period. Such a methodology leads to deviation of the actual percentage of cases included below the *n*th centile from the calculated rate. However, for large number of analyses the mean of this deviation approaches zero. Meyer *et al.* (1988) present five such analyses, one for each 3-year period. The actual percentage of newborns included under the calculated 10th centile ranged from 11·2% to 8·5% and showed a secular trend. Erroneously, this led them to conclude that the rate of newborns included under the 10th centile had significantly decreased by 20%. Furthermore, they attributed this to the improved antenatal care which their institute provides.

Taking this *ad absurdum* one is led to conclude that with proper treatment and prenatal care the percentage of newborns under the 10th centile can be further reduced. This is a paralogistic conclusion, because there will always be 10% of observations under the 10th centile. Therefore, the main observation of this report is an artefact created by inappropriate application of methods. Statistical methods are used to investigate trends within given biological, medical, or sociological systems. There is always the possibility that the characteristics of a population's distribution are changing with time. This justifies a constant effort towards better understanding of these trends. However, investigators should not be carried away by the magic of statistical methods to believe that 100% can be calculated to equal 105%.

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Meyer L., Bouyer J., Papiernik E., Le Lann D., Moukengue L & Dreyfus J (1988) Secular trend in the rate of small-for-gestational-age infants Haguenau Study 1971–1985. *Br J Obstet Gynaecol* **95**, 1257-1263.

Dear Sir,

We were very interested to read the article by Meyer *et al.* [*Br J Obstet Gynaecol* (1988) **95**, 1257–1263]. There is a strong tendency among health professionals to relate causally secular trends in perinatal outcome to the type and quality of care that they provide. This has been noted for perinatal mortality (Keirse 1984*b*), for survival of the tiny infant (Stewart *et al.* 1981), and now also for the rate of 'small-for-gestational-age' infants (Meyer *et al.* 1988).

Meyer *et al.* (1988) attributed changes in the rate of infants <10th centile born in Haguenau, France, between 1971 and 1985, to earliness of prenatal care. Although the authors admit that further research is necessary 'to *confirm* the influence of prenatal care on the rate of small-for-gestational-age babies', the inference is that early attendance for prenatal care (and possibly the Haguenau preterm prevention programme) results in a lower incidence of light-for-gestational-age infants than late attendance for care.

Assuming that both trends are real and that they are causally related, it does not necessarily follow, as Meyer *et al.* (1988) infer, that earlier prenatal care leads to a heavier baby at a given gestational age. A major effect of early *versus* late attendance for care is that the exact duration of gestation can be determined more accurately in early than in late pregnancy. This well-known principle applies to all methods of determining gestational age, irrespective of whether they are based on the woman's recollection of the last period, clinical examination, biochemical tests or ultrasound measurements. It implies that, in comparison to early attenders, a group of late attenders delivered at a particular gestational age will contain more women whose actual duration of pregnancy is shorter or longer than the estimated duration. It follows that these late attenders are more likely to give birth to an infant estimated to be of low-weight-for-gestation, not because of low weight, but because pregnancy was judged to be more advanced than it is in reality.

The effects of this phenomenon are illustrated in Fig. 1, which represents hypothetical cohorts of 30 infants each, born at a particular week of gestation in four successive periods during which accuracy of gestational age estimation increases. Increased accuracy with time (exaggerated in

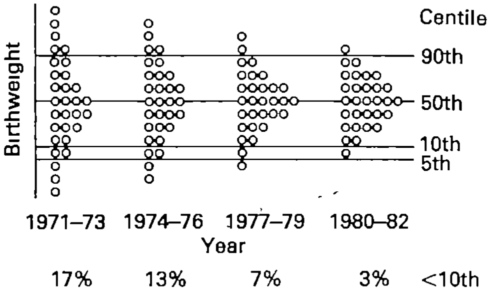

Fig. 1. Distribution of birthweights and centiles of weight for gestation across four periods characterized by increasing accuracy of gestational age estimation (30 infants per period).

the Figure) can, as mentioned, result from earlier attendance for care, but also from more judicious use of early ultrasound to ascertain gestational age. The latter trend is likely to have occurred from 1971 to 1982 and has been shown to have this effect in controlled trials in that it reduces the incidence of induction of labour for post-term pregnancy (Bakketeig *et al.* 1984; Eik-Nes *et al.* 1984). The model shows that common centiles for the entire group of infants, as used by Meyer *et al.* (1988), automatically reduce the incidence of birthweights <10th centile when gestational age estimates become more precise. The Figure also explains two further effects that were reported by Meyer *et al.* (1988). First, the increase in accuracy of gestational age estimation reduces the proportion of infants <5th centile among infants <10th centile. Second, despite a marked decrease in the incidence of light-for-gestational-age infants, there is no secular trend in mean or median birthweight.

The above invites the conclusion that Meyer *et al.* (1988) described a secular trend not in birthweight-for-gestation but in the cut-off points applied to it. Unfortunately, they did not examine whether early attendance also decreased the incidence of heavy-for-gestational age infants (Fig.1). If they had, they might have produced a useful hypothesis rather than an illustration of one of the known artefacts of weight-for-gestational-age curves (Wilcox 1981; Keirse 1984*a*).

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Authors' reply

Dear Sir,
We would like to thank Dr Ben-Shlomo for his letter which gives us the opportunity to emphasize two important points.

In our survey, the birthweight centiles were computed from all the livebirths of the 15-year study period, i.e. from 1971 to 1985 (see Patients and methods section). We performed *one* analysis and not 'five such analyses, one for each 3-year period' as stated by Dr Ben-Shlomo. Therefore, centiles ranged from 11·2% to 8·5% because of time trends and not because of statistical fluctuations due to the method's lack of precision. We used our own birthweight standards as explained in the paper, but we checked that a decline in the rate of small-for-gestational-age (SGA) infants would also have been observed if other published standards had been applied (Lubchenco *et al.* 1963; Leroy & Lefort 1971). These other standards did not completely fit our data, either because they had been

Table 1. Secular trend in the rates of small-for-gestational-age (SGA) and heavy-for-gestational-age (HGA) infants, 1971–1983

	1971–73	1974–76	1977–79	1980–82	1983–85
HGA rate	11·1%	11·6%	9·5%	10·3%	8·4%
SGA rate	11·2%	10·1%	10·3%	8·5%	9·2%

derived from a population of much lower weight, or because they did not account for sex.

Finally, we did not 'attribute' the decrease in the SGA rate to improved neonatal care, as stated by Dr Ben-Shlomo. In such an observational study, we only *observed* an association (previously observed by some other authors) and *suggested* further research to confirm the influence of prenatal care on the rate of SGA babies.

We would also like to thank Dr Keirse for his very interesting and stimulating remarks about our paper. If his hypothesis was correct, we should have observed in our study a decrease with time in the rate of heavy-for-gestational-age infants (HGA), which would be parallel to the SGA rate. Our actual results are shown in Table 1.

The HGA rates for the period 1971 to 1982, during which the most important decrease in the SGA rate occurred, do not indicate a similar decline. Moreover, as indicated in our paper, there was a decrease in the rates of low- and very-low-birthweight infants, as well as a reduction in the dispersion of birthweight: these changes cannot in any way be attributed to changes in estimation of gestational age, but support the hypothesis that 'something' did happen. Most importantly, in contrast to the SGA rate, the HGA rate was not associated with the time of the first consultation at the Maternity Hospital; the HGA rates for first, second and third trimester presentations were 10·0%, 9·6% and 10·5%, respectively, and 10·7% for women who came in only for the delivery ($\chi^2=3{\cdot}5$, d.f.$=3, P=0{\cdot}32$). The corresponding values for the SGA rate were, respectively, 8·5%, 10·4%, 10·8% and 12·1% ($\chi^2=33{\cdot}4, P<10^{-6}$). For these reasons, we think our data show a real effect and are not artefactual.

We would like to develop another point. Dr Keirse suggests that the error in the estimation of gestational age is randomly distributed. This assumption may not be true. Several authors (Belfrage *et al.* 1987; Bennet *et al.* 1982) using ultrasound measurement in early pregnancy have observed that in 16–20% of pregnancies there was a need to correct the estimated date of delivery. If only the date of the last period had been available the duration of gestation would have been overestimated in 13–16% and underestimated in 3–4% of pregnancies. It follows that a lack of ultrasound information would lead to overestimation of the length of pregnancy in about 10–12%. The risk of overestimation of the prevalence of SGA was studied by Bennet *et al.* (1982). They found that, despite a 10% frequency of overestimation of length of pregnancy, the SGA rate in the group of babies where the results of echography were withheld (8·3%) was quite similar to that in the group where the results were known (9%). It is important to remember that overestimation of the length of pregnancy does not lead automatically to the classification of the baby as SGA. Only a very small proportion of misclassified babies will be light enough to be erroneously classified as SGA. Thus, it is very unlikely that this type of error, if it occurred at the beginning of the Haguenau study, could explain quantitatively all the observed decrease in the SGA rate.

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BOOK REVIEWS

Obstetric Anesthesia by Sivam Ramanathan. Lea & Febiger, Philadelphia, 1988, 420 pages with figures and tables, $45.00

This book is not, as its name implies, a manual of how to do it, but offers a review of obstetric anaesthesia in many situations. To that end it is divided into three sections.

The first deals with normal pregnancy and has several excellent chapters on maternal adaptation to pregnancy, function of the placenta and the alterations in drug pharmacokinetics and dynamics occasioned by this condition. The chapters on anaesthesia for labour and caesarean sections are well thought out but perhaps a little brief.

The second section is devoted to a consideration of high-risk pregnancy and the obstetric anaesthetists's role therein. The author has produced a well-researched and comprehensive account of the many conditions which may coexist with or be caused by the pregnant state, and this is a section which can be read with profit by even the most experienced of practitioners. Of course there are chapters on pre-eclampsia, coagulation and haemoglobin disorders, diabetes and also cardiac disease. Other accounts are of endocrine disease, asthma, thromboembolus and neurological disease. Difficult obstetric situations, renal disease, drug abuse and anaesthesia for non-obstetric complications complete this excellent and always readable book. In addition, the illustrations which are a feature of the book are always absolutely first class.

The final section is devoted to the fetus, with chapters on fetal well-being, neonatal resuscitation, prematurity and neonatal emergencies. This is of course not normally the anaesthetist's brief but it is no bad thing to be fully informed and from time to time it is necessary for the obstetric anaesthetists to come to the aid of a junior paediatrician involved in a difficult resuscitation.

In summary, this is a book that should grace the shelves of every anaesthetic department involved in the provision of maternity services; and few specialist obstetric anaesthetists would regret purchasing a copy.

K. G. A. Macleod

Clinical In Vitro Fertilization. Second edition edited by Carl Wood & Alan Trounson. Springer Verlag, London, Berlin, Heidelberg, New York, 1988, 166 pages with figures and tables, £36.50

The 5-year interval since publication of the first edition has witnessed a remarkable worldwide increase in the number of IVF/GIFT units. A great deal of experience has been acquired during this time, and while some may regard this book as being too parochial (and undoubtedly it could have been improved with more rigorous editing) it contains much valuable information and is a worthy successor to the first edition.

The first three sections cover patient selection and preparation for IVF, induction of ovulation and oocyte recovery. The information is of limited use to established units although comparison to and possible improvements to existing protocols and routines is always possible. The information would be extremely useful to new units.

Dr Trounson's two chapters covering embryo culture and cryopreservation are without doubt essential reading to both clinicians and laboratory scientists. The information is highly pertinent and there are few practitioners who will not gain from careful perusal of his writings.

The outcome of treatment is subdivided into two chapters, the first dealing with the results from in-vitro fertilization, and the second the outcome of pregnancy. The information forms a valuable source of material, and the data concerning the increased perinatal loss associated with the high rate of multiple pregnancies pose serious practical and ethical questions relating to the number of eggs/embryos replaced.

The chapter on gamete intrafallopian transfer could have been shortened as the information on anaesthesia is basically of research rather than of clinic interest.

The section dealing with andrology, male factors and IVF contains a great deal of information, but in contrast to Dr Trounson's fluent style of writing this chapter does not make easy reading.

Dr Chen's chapter dealing with oocyte freezing adequately covers this aspect of the field with clarity and brevity as do the two final chapters on oocyte donation and infertility counselling.

B. A. Lieberman

The 1988 Year Book of Perinatal/Neonatal Medicine by Marshall H. Klaus & Avroy A. Fanaroff. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 334 pages, £33.00

Year books are both useful and dangerous: useful because they are a convenient way of catching up with some of the interesting papers that one has missed (for example this year book quotes from 64 journals); dangerous because they present a pre-digested interpretation from which there is no way of assessing the reliability of the original data. Thus one is very dependent upon the skill of the editors in their choice and editing of the material presented. In the case of this volume, the editors and discussants are all very reputable and their comments are interesting and helpful. Nonetheless, one must guard against the temptation to use the abridged versions in the year book as a definitive source and always consult the original paper before referring to its data and conclusions in one's own work. I find that in a significant proportion of papers my own interpretation of the original will differ from that of an editor, however eminent he may be.

Many topics are covered, ranging from cordocentesis and Doppler velocimetry through antenatal screening, infectious diseases, immunology and nutrition, to neonatal neurology, gastroenterology, cardiology and pharmacology. There is something for everyone interested in perinatal medicine. Most of the extracts are about one page long, and thus make ideal reading during a visit to the smallest room. And perhaps this is the best place for such a book, for it is essentially an ephemeral volume, serving to draw one's attention to papers which one wishes to investigate in the original, rather than making any substantial contribution of its own.

P. J. Steer

Progress in Obstetrics and Gynaecology Volume 7 edited by John Studd. Churchill Livingstone, Edinburgh, 412 pages with figures and tables, £19.95

It has been said many times that if *Progress in Obstetrics and Gynaecology* did not exist, then it would have to be invented. This is surely an excellent accolade for what is now becoming a permanent part of British and Commonwealth postgraduate obstetrics and gynaecology. John Studd's initial idea was certainly novel and not before its time. It has generated six previous volumes on varied subjects, all considered in a most professional manner. Volume 7 is no exception.

Each volume runs to a set format and that is divided into both an obstetric and a gynaecological section. There are about 12 to 13 subjects covered in each text. These are of contemporary interest and are usually considered not only by experts in the field, but also by 'up-and-coming' authorities. The latter tend to write with enthusiasm and with knowledge that sometimes exceeds that of more senior authors. The result is a mixture of both enthusiasm and authority.

In this specific volume, the obstetrics section covers such subjects as fetal allograft survival and maternal blood supply to the placenta. Sections on gene probes and cordocentesis by recognized experts are included. Social subjects like schoolgirl pregnancy and high-risk pregnancy and maternal narcotic addiction are also covered. Intrauterine death, failed forceps, and the very-low-birthweight babies are considered in very general and specific terms. It is hard to pick faults with any of these chapters and all are of interest.

The gynaecology section again looks at contemporary subjects. Videolaseroscopy for the treatment of endometriosis catches one's eye as does the chapter on hysteroscopy and gamete intrafallopian tube transfer. Contentious subjects such as the sex ratio and ways of manipulating it head the gynaecology section. The oncology section relates, essentially, to premalignant disease of the lower genital tract and here there is a professionally written chapter on colposcopy and cervical adenocarcinoma. Preinvasive disease of the vulva completes the section.

This volume maintains the same high standard as in the previous six. Overall the chapters are well set out and there are plenty of appealing headings and subheadings as well as clear charts and figures. I believe that this volume, like its predecessors, should be an integral part of every postgraduate's library. Certainly consultants would do well to keep up to date by reading it.

Albert Singer

Books received some of which may be reviewed at a later date

Medical Disorders in Obstetric Practice Second edition edited by Michael de Swiet. Blackwell Scientific Publications, Oxford, 1989, 854 pages with figures and tables, £49.50

Textbook of Pain Second edition edited by Patrick Wall & Ronald Melzack. Churchill Livingstone, Edinburgh, London, 1989, 1084 pages with figures and tables, £95.00

A Colour Atlas of Gynaecological Cytology by O. A. N. Husain & E. Blanche Butler. Wolfe Medical Publications Ltd, Ipswich, 1989, 128 pages fully illustrated with colour plates, £40.00

Intrauterine Growth Retardation: A Practical Approach by Thomas L. Gross & Robert J. Sokol. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1989. 237 pages with figures, tables and photographic plates, £31.00

Diseases of the Fetus and Newborn. Pathology, Radiology and Genetics edited by G. B. Reed, A. E. Claireaux & A. D. Bain. Chapman & Hall Medical, London, 1989, 812 pages with figures, tables and photographic plates, £135.00

Before We Are Born. Basic Embryology and Birth Defects. Third edition by Keith L. Moore. W. B. Saunders Company, Philadelphia, London, Toronto, 1989, 306 pages fully illustrated, £15.95

Baillière's Clinical Obstetrics and Gynaecology. International Practice and Research. Vol. 3/ No. 1, March 1989, Operative Treatment of Ovarian Cancer edited by E. Burghardt & J. M. Monaghan. Baillière Tindall, London, Philadelphia, 1989, 215 pages with figures and tables, £18.50

Having a First Baby. Experiences in 1951 and 1985 Compared by Barbara Thompson, Cynthia Fraser, Angela Hewitt & Debbie Skipper. Aberdeen University Press, 1989, 184 pages with figures and tables, £14.50

Obstetrical Pearls: A Practical Guide for the Efficient Resident by Michael D. Benson. F. A. Davis Co., Philadelphia (distributed by Quest Meridien Ltd, Kent), 199 pages with figures and tables, £7.97

The Well Woman Handbook by Suzie Hayman. Penguin Books, London, 1989, 182 pages illustrated, £3.99

Nursing Care During the Labor Process Third edition by Janet S. Malinowski, Carolyn G. Pedigo & Celeste R. Phillips. F. A. Davis Co., Philadelphia, 1989, 433 pages, £12.03

Learning Medicine 1989 by Peter Richards. British Medical Association, London, 1989, 98 pages, £3.95

Cancer Surveys. Advances and Prospects in Clinical, Epidemiological and Laboratory Oncology. Vol. 7 No. 3, Prospects for Primary and Secondary Prevention of Cervix Cancer edited by G. Knox & C. Woodman. Published Quarterly for the Imperial Cancer Research Fund by Oxford University Press, Oxford. Annual subscription £53.00 UK; $110.00 North America; £64.00 elsewhere; single issue £15.00

The Reproductive Health of Adolescents. A Strategy for Action A Joint WHO/UNFPA/UNICEF Statement, 1989, WHO, Geneva, Sw. fr. 3.00

Multimodal Treatment of Ovarian Cancer (Monograph Series of the European Organization for Research and Treatment of Cancer Vol. 20) edited by Pier Franco Conte, Riccardo Rosso, Nicola Ragni & Jan B. Vermorken. Raven Press, New York, 1989, 351 pages with figures and tables, $111.50

Symposium

Preservation of the Tubo-Ovarian Function in Gynecologic Benign and Malignant Diseases edited by K. Ichinoe, S. J. Segal & L. Mastroianni. Serono Symposia Publications, Volume 48, Raven Press, New York, 1989, 680 pages with figures and tables, no price given

New Journal

Obstetric/Gynecology Report. Vol. 1 No. 1, 1988 edited by Frederick P. Zuspan. C. V. Mosby Co., Missouri, annual subscription $52.50 US and $58.00 Canada and international

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COMMENTARIES

Intrauterine growth retardation: Let's be clear about it

'The words used in clinical medicine have a tremendous influence on the subject they describe or purport to describe. They perpetuate illnesses, syndromes and signs whose existence is doubtful, they deny recognition to others whose existence is beyond question and, moreover, they distort textbook descriptions to conform to the chosen word'.

That admonition by Asher (1972) is particularly appropriate to a discussion of the widely misused term 'intrauterine growth retardation'. To retard is to delay progress which, in the context of fetal growth, implies an imposed reduction of growth, a downward inflexion from the normally steady progression. It is abnormal.

In clinical practice, and often in papers submitted to this journal, fetal growth is confused with fetal size and it is common for 'birthweight-for-gestational-age' standards to be described as 'fetal growth charts', and a weight-for-gestation below some arbitrary centile to be referred to as 'intrauterine growth retardation'. The distinction between size and growth is critical. Growth cannot be estimated from less than two measurements of size, and the argument that size at some time in late pregnancy and a presumed zero size at conception can represent those two measurements is both philosophically dubious and clinically unhelpful. What the clinician needs to know is whether fetal growth has deviated from its normal progression.

A single estimate of fetal size in late pregnancy is of little or no help to the obstetrician. The arbitrary categorization of all babies estimated to be below the 10th or 5th centile for gestational age as 'growth retarded', and therefore abnormal and in some jeopardy, is highly misleading. If a single estimate of fetal size in late pregnancy suggests an unusually small baby, then the clinician might assume that some pathological interference with growth has occurred; but the size alone does not prove it. It must not be forgotten that in any population of fetuses some 10% will, by definition, have a weight below the 10th centile, and it is absurd to define in advance the proportion of babies that will suffer from a pathological 'growth retardation'. The term 'intrauterine growth retardation' should be restricted to those fetuses where there is definite evidence that growth has faltered, or to instances where clinical evidence points to loss of fetal weight *in utero*. Such infants may not necessarily be 'light-for-gestational-age'; a fetus whose weight has fallen from the 90th centile to the 30th in a short time is almost certainly in greater peril than a fetus who has maintained a position on the 5th centile. These may be seen to correspond to two different types of intrauterine growth retardation, often referred to as asymmetrical (or disproportional, or late-flattening), and symmetrical (or proportional, or low profile). Asymmetrical growth retardation is characterized by a rapid slowing of growth near term, whereas symmetrical growth retardation indicates consistent suboptimal growth. It will be obvious that symmetrical growth retardation due to some pathological process cannot be distinguished on the basis of size alone from the lower ranges of normal growth.

The estimation of growth rather than size is important, because the object of antenatal surveillance is to anticipate or demonstrate clinical problems that can be helped by appropriate action. Establishing that a fetus is small does not establish a clinical problem; only the demonstration of impaired growth can do that. That basic point has been recognized by those studying child growth, but not usually by those studying fetal growth.

In the burgeoning field of fetal medicine it is increasingly necessary to have a policy of unequivocal agreed terminology, allied to a clear view of what is currently possible in experimental studies. In the study of any circumstances which may be related to fetal well-being, from Doppler ultrasound measurements of umbilical blood flow to measures of maternal nutrition, the commonest outcome variable is 'fetal growth'. Almost invariably, and perforce, this is taken as some index of birthweight-for-gestation such as a centile from some published though not necessarily appropriate standard. And that is all it is; we cannot make any inference about 'growth retardation' from such data.

The concept underlying that approach is that there is a clear dichotomy between 'normal' and 'abnormal' fetuses. While such dichotomization of continuous variables to define disease is common in clinical practice (for example in defining hypertension and anaemia) it can be seriously misleading. Risk increases in a continuous, though not necessarily linear, manner with decreasing size, however measured; it does not suddenly occur below some arbitrarily defined threshold.

There is now an urgent need to establish true measures of fetal growth from which deviations indicating genuine growth retardation can be derived. Ultrasound techniques have the capacity to detect abnormalities of fetal growth but have not been effectively exploited. We now need prospective studies to examine the differential growth of fetal parts, say head, abdomen and femur, in large samples to see whether patterns of growth that are associated with fetal compromise and later infant morbidity can be defined. Such studies must be performed with scheduled repeat measurements, and it is particularly important that some reliable measures of outcome should be established. Interventions based on estimates of size or growth should be assessed in randomized trials before they are implemented in general obstetric practice.

Meanwhile much confusion in the literature can be avoided by stating clearly only what has been observed in the fetus or newborn infant. If it is small for its gestational age in relation to some stated standard, say so; if there is evidence that growth has been impaired or is abnormal, then give that evidence.

A fuller review and discussion of these issues has been published by Altman & Hytten (1989).

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Infection and preterm birth

The incidence of preterm birth in Britain and America has not changed for 25 years (Agustsson & Patel 1987; Martius *et al.* 1988). About 6–8% of pregnancies still end in preterm delivery (Hewitt & Newnham 1988) and, although advances in neonatal care have improved the chances of survival for small babies, about 70% of perinatal mortality in developed countries is still associated with immaturity (Hibbard 1987; Newman 1988; Hatjis & Swain 1988). Many of these deaths may be unavoidable, for example because of lethal malformations or intrauterine death (King *et al.* 1988), but theoretically about a third of deaths associated with immaturity are preventable.

Iams (1988) has argued that the principal task facing today's obstetricians is the prevention of prematurity, but that 'nonetheless we continue to fiddle while our biggest source of perinatal mortality burns unattended'. Our failure to reduce the incidence of preterm birth, however, has not been for want of research. Most spontaneous preterm labours are not due to a recognizable cause (Hibbard 1987). Nevertheless, evidence for a link between preterm labour and infection is accumulating from epidemiological, microbiological and biochemical studies.

Recent epidemiological work has shown a connection between preterm delivery and a history of infection. A prospective study in New

York found strong correlations between preterm birth and both a history of pelvic inflammatory disease and a history of intrauterine contraceptive device usage (Toth *et al.* 1988). Premature rupture of the membranes was correlated with a history of multiple sex partners. Mimouni *et al.* (1988) reported that 30% of diabetic women experience spontaneous preterm labour: it is associated with poor glycaemic control and strongly associated with vaginitis, cystitis, or both.

The organisms commonly associated with chorioamnionitis are those normally found in the lower genital tract during pregnancy (Hurley 1988). Colonization with group B streptococci is associated with preterm premature rupture of the membranes (PPROM) (Hibbard 1987). In studies in the USA, non-specific vaginitis and chlamydial infection were each associated with preterm labour (Martius *et al.* 1988) and with PPROM (Gravett *et al.* 1986). In a British study, high vaginal swabs from women admitted in spontaneous preterm labour were more likely to show ureaplasmas, *Mycoplasma hominis* and chlamydia than those from women requiring preterm delivery for other reasons (Lamont *et al.* 1987). Romero *et al.* (1989*a*), however, concluded that the weight of published evidence does not support an association between prematurity and genital colonization with mycoplasma.

Hillier *et al.* (1988) carried out microbiological and histological examination of the placenta and chorion after preterm delivery and delivery at term. They isolated micro-organisms (mainly *Ureaplasma urealyticum* and *Gardnerella vaginalis*) from 61% of placentas from women who were delivered before 37 weeks gestation but from only 21% of women without preterm labour. Isolation of organisms was strongly associated with histological chorioamnionitis, and the proportion of placentas with evidence of infection was highest among those who were delivered at the lowest gestational age. Placental inflammation is rare in uncomplicated term pregnancy (Salafia *et al.* 1989*b*).

Recent reports have linked preterm delivery with listeriosis (Valkenburg *et al.* 1988), *Haemophilus influenzae* (Winn & Egley 1987), *Propionibacterium acnes* (Reed *et al.* 1988), *Capnocytophaga* (McDonald & Gordon 1988), fusobacteria (Altshuler & Hyde 1988) and *G. vaginalis* (Moran & Payne 1989). Preterm labour is reported to be associated with higher vaginal pH values than labour at term (Gleeson *et al.* 1989): a rise in pH may indicate reduced numbers of lactobacilli, which may be either a cause or a consequence of infection. Studies of amniotic fluid obtained by amniocentesis after premature rupture of the membranes have shown that women in labour have a higher chance of a positive culture and higher concentrations of bacterial endotoxin than those not in labour (Romero *et al.* 1988*b, c*). The onset of labour associated with chorioamnionitis has a different circadian rhythm from normal labour (Cooperstock *et al.* 1987).

Such associations do not prove that infection causes preterm labour, but a causative link is plausible. The endocrine or paracrine factors that initiate labour are unknown but prostaglandins probably play a prominent role, and the amnion is an important site of prostaglandin (PG) production (López Bernal *et al.* 1987*a*). In-vitro production of PGE is low in amnion obtained after uncomplicated preterm deliveries compared with that obtained after spontaneous delivery at term (López Bernal *et al.* 1987*a*) but acute chorioamnionitis causes a huge increase in PG production which could cause preterm labour (López Bernal *et al.* 1987*b*). As well as producing prostaglandins, amnion affected by inflammation may produce increased amounts of proteases and platelet-activating factor, which may be involved in the initiation of labour (McGregor 1988). Bacterial endotoxin may stimulate decidua to produce interleukin-1, which is capable of stimulating PG release (Romero *et al.* 1989*b*). Bacteria themselves may produce enzymes which can focally weaken the amniochorion and predispose to premature rupture of the membranes (McGregor 1988, Lonky & Hayashi 1988).

Better understanding of the link between infection and preterm labour could help clinicians in various ways—by allowing us to prevent preterm labour or by improving our treatment of established preterm labour. Prevention, however, remains difficult. Many of the organisms implicated in causing preterm labour are common and difficult to eradicate. It has been suggested that a policy of energetic treatment of vaginitis, cervicitis and urinary infection could reduce the occurrence of preterm labour (Iams 1988), but whether prophylactic antimicrobial therapy can prevent preterm delivery remains doubtful (Editorial Comment 1989).

Much recent research on the management of

PPROM or preterm labour has concentrated on the early identification of infection. Amniotic fluid can be obtained by amniocentesis after PPROM or during preterm labour, and examined by Gram staining for bacteria (Romero *et al.* 1988*a*) or gas-liquid chromatography for bacterial products (Romero *et al.* 1988*d*). Other investigators have measured the concentration of bacterial endotoxin (Cox *et al.* 1988) or leukocyte esterase (Egley *et al.* 1988). Intrauterine inflammation may also be associated with abnormal fetal heart rate patterns (Salafia *et al.* 1989*a*), oligohydramnios or a lack of fetal breathing movements (Fisk 1988).

Serum markers have also been investigated as a means of early detection of infection, and most research has concentrated on C-reactive protein (CRP), a globulin of hepatic origin which rises in the acute phase of any active infection. Fisk *et al.* (1987) measured serum levels at daily intervals in women with PPROM and found that consecutive values over 20 mg/l appeared highly predictive of infection. Cammu *et al.* (1989) found that elevated CRP levels were correlated with histological evidence of placental infection and were more often found in patients refractory to tocolysis, but they concluded that CRP has little clinical relevance because raised levels do not predict perinatal infection and do not alter clinical management. By contrast, Moran & Payne (1989) reported a case in which raised CRP levels aided clinical management: amniocentesis led to the diagnosis of intrauterine infection with *G. vaginalis* and a caesarean section with a successful outcome. It has been claimed that raised serum CRP in the newborn is a predictor of neonatal infection (Salzer *et al.* 1987), but this has been disputed (Fisk & Fysh 1988).

Obstetricians tend to undervalue antibiotic treatment in PPROM and preterm labour (Trudinger & Boshell 1987). The consensus among Swedish obstetricians is that in PPROM antibiotic prophylaxis cannot be recommended as a routine (Olofsson *et al.* 1988). In the USA, however, a recent randomized study showed that after PPROM, ampicillin prophylaxis can reduce the risk of preterm delivery and the frequency of neonatal infection (Amon *et al.* 1988), and another American study has concluded that antibiotic therapy in idiopathic preterm labour can significantly prolong pregnancy (Morales *et al.* 1988). If infection occurs in preterm labour, treatment with antibiotics should be started immediately and not delayed until after delivery (Gibbs *et al.* 1988; Gilstrap *et al.* 1988; Olofsson *et al.* 1988). The commonest sign of intrapartum infection is pyrexia, but it should be borne in mind that maternal temperature may rise as a result of epidural analgesia (Fusi *et al.* 1989).

In Japan an indwelling cervical catheter for use in PPROM has been assessed in a large collaborative study (Ogita *et al.* 1988). Its purpose is to plug the membranes, preventing loss of amniotic fluid, and to allow the infusion of sterilizing solution and antibiotics. This treatment can reduce the frequency of positive amniotic fluid cultures, but its effectiveness has not yet been assessed in a randomized trial.

Although we are still some way from understanding the detailed mechanism of preterm labour, Iams (1988) has argued that prevention of preterm delivery need not await full understanding of its cause. Initiatives to try and reduce the occurrence of immaturity have been taken in several countries. Programmes of education about premature labour have been associated with a reduction in the incidence of low birthweight babies in North Carolina (Covington *et al.* 1988) but not in California (Konte *et al.* 1988). In France, obstetricians are being encouraged to carry out vaginal examination at each antenatal visit in an effort to identify early signs of preterm labour. British obstetricians may suspect that such examinations risk provoking labour, but the value of this programme is being tested in a randomized trial, the results of which are expected in 1990 (Blondel *et al.* 1988).

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Prostaglandin E production by the fetal membranes in unexplained preterm labour and preterm labour associated with chorioamnionitis

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Summary. The production of prostaglandin E (PGE) by amnion, choriodecidua and placenta was measured in 45 women delivered after spontaneous preterm labour, in 10 women delivered electively preterm, in 30 women at elective caesarean section at term, and in 28 women after spontaneous labour at term. In the preterm labour group 24 women had normal placental histology, and gestational age was 34 (31–36) weeks (median and range); 18 women had evidence of chorioamnionitis and gestational age was significantly shorter, 30 (24–36) weeks; three other patients had placental abruption. In the absence of inflammatory infiltration of these tissues the highest PGE output (fmol/mg dry weight/2 h) was found after labour at term and the lowest after uncomplicated preterm labour: 2640 (360–15 580) (median and range) compared with 1414 (164–11 045) in amnion, 677 (100–3245) compared with 308 (39–1086) in choriodecidua, and 1200 (520–3022) compared with 578 (150–1859) in placenta, respectively. Tissues showing chorioamnionitis produced much higher outputs of PGE from amnion (12 278, 1799–82 617) and from choriodecidua (1018, 216–11 768), but not from placenta (616, 89–4131). Chorioamnionitis seems to cause very early preterm labour by increasing PG production in the amnion and choriodecidua.

Preterm labour remains a major cause of perinatal mortality and morbidity but little progress has been made in understanding its cause. Prostaglandins (PGs) are involved in the onset and progress of labour at term, and increased PG production by intrauterine tissues (placenta, fetal membranes) is a key factor (Keirse 1979; Mitchell 1986). PGs stimulate contractility in the human pregnant uterus both *in vivo* and *in vitro* (Karim & Hillier 1979), and high-affinity PGE receptors are present in human myometrium throughout gestation (Bauknecht *et al.* 1981; Adelantado *et al.* 1988). Preterm labour can be uncomplicated, occurring without obvious cause, or complicated and associated with disorders such as intrauterine infection or antepartum haemorrhage. In preterm labour complicated by chorioamnionitis, there is a higher level of PGE production by the amniotic

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epithelium than in spontaneous labour at term (López Bernal *et al.* 1987*a*), while in uncomplicated preterm labour, by contrast, amniotic PGE output is lower than in spontaneous labour at term (López Bernal *et al.* 1987*a*). The purpose of this paper was to investigate PG output by the placenta and choriodecidua, as well as the amnion, and to examine the frequency of chorioamnionitis at various gestational ages. Additional observations have also been made on the rate of PGE production by these tissues before and during labour at term and preterm.

Subjects and methods

Placentas and fetal membranes were obtained from 45 women delivered after spontaneous preterm labour between 24 and 36 weeks gestation. The only patients excluded were those with multiple pregnancies or fetal abnormalities. Three women had had antepartum haemorrhage with proven placental abruption or placenta praevia and were analysed separately. Of the remaining 42 patients, seven were delivered by emergency caesarean section because of fetal distress, breech presentation, cord prolapse or a combination of these factors. The other 35 patients had vaginal deliveries. On the basis of histological examination (see below) patients were classified as having normal placentas, group A (n = 24), or as showing evidence of inflammatory changes, group B (n = 18). In the latter group two women had had small antepartum haemorrhages but no evidence of abruption or placenta praevia. In each of these two groups, five women had premature rupture of the membranes. Tissues were also collected from 10 women delivered preterm electively by caesarean section for severe pre-eclampsia (group C); from 30 women delivered before labour, at term, by elective caesarean section for a variety of reasons including previous section or malpresentation (group D); and from a group of 28 women after spontaneous labour and vaginal delivery at term (group E). All women were delivered of live fetuses but three babies in group B died within 24 h of delivery (further clinical details in Table 1). Placental villi from early pregnancy were obtained from five women who had a surgical abortion at 6–10 weeks gestation. These studies had the approval of the Central Oxfordshire research ethics committee.

Tissues were examined histologically in all cases (Zaaijman *et al.* 1982). Blocks of placenta were cut so as to include both fetal and maternal surfaces; samples of fetal membranes were obtained from the placental and peripheral part of the amniotic sac and a length of umbilical cord was also taken, from the placental end. Tissues were examined for polymorphonuclear leucocyte infiltration, other cellular infiltrates and evidence of inflammation. Histological examination was performed without knowledge of the PG assays.

Discs of amnion and choriodecidua were prepared as described previously (López Bernal *et al.* 1987*b*). Slices were prepared from the central part of the placenta after removing the decidual plate. Incubations were made in triplicate in a final volume of 2 ml of pseudoamniotic fluid

Table 1. Clinical data for the five groups in the study*

	Group A (n = 24)	Group B (n = 18)	Group C (n = 10)	Group D (n = 30)	Group E (n = 28)	P value
Maternal age (years)	24(17–39)	27(17–42)	31(23–41)	27(16–35)	28(21–40)	NS
Parity	0(0–2)	0(0–4)	1(0–4)	2(0–3)	1(0–3)	<0·02
Gestation (weeks)	34(31–36)	30(24–36)	34(26–36)	39(38–41)	40(38–42)	<0·001
Apgar score at 5 min	10(3–10)	8(4–10)	10(5–10)	10(8–10)	10(9–10)	<0·01
Birthweight (kg)	2·4 (1·5–2·8)	1·5 (0·5–2·8)	1·8 (0·6–2·8)	3·2 (2·3–4·2)	3·4 (2·7–4·6)	<0·001
Length of labour (h)†	6·4 (1·5–11·1)	4·7 (2·0–11·8)	—	—	5·6 (1·4–16·3)	NS

Results are medians and ranges

P values from Kruskal–Wallis test. NS, Not significant, P>0·05.

*Group A. Spontaneous preterm labour, normal placental histology, Group B: spontaneous preterm labour, inflammatory changes in placenta; Group C: elective preterm caesarean section for severe pre-eclampsia; Group D: elective section at term for a variety of reasons, Group E spontaneous labour at term with vaginal delivery.

†Excluding 5 patients in group A and 4 in group B who were delivered by emergency section and/or had tocolytics.

Table 2. Histological findings in the 18 patients in group B (preterm labour with inflammatory changes)

Gestation (weeks)	Funisitis	Chorio-amnionitis	Inter-villositis	Deciduitis	Other pathology	Organism*
24	Present	Focal	Adj.chor. plate	Extensive +micro-abscesses	—	*L.monocytogenes*
24	Present	Extensive	Adj.chor. plate	—	Retroplacental haematoma	Not done
24	—	Extensive	Adj chor. plate	Present uniform	—	No pathogens
25	—	Mild	—	—	—	Not done
25	—	Focal round-cell infiltrate	—	—	Haemorrhage	Group B β-haem.strep.
26	Present	Extensive	—	—	—	Group B β-haem.strep.
26	Present	Extensive	Adj.chor. plate	Present uniform	Chorionic plate vasculitis	*Staph.aureus* profuse
27	Present	Extensive	Adj.chor. plate	—	—	Anaerobes
29	Present	Extensive	—	—	—	Not done
30	Present	Extensive	Adj.chor. plate	—	Chorionic plate vasculitis	Not done
32	—	Mild	—	—	—	Not done
32	—	Focal round-cell infiltrate	—	—	—	Not done
34	—	—	—	—	Focal villitis	*Strep milleri*
35	—	Mild	—	—	—	*C albicans* 2/2
35	—	—	—	Extensive acute/ chronic	—	No pathogens
35	—	—	—	Focal chronic	—	Not done
35	—	—	—	—	Focal villitis	Not done
36	—	—	Focal	—	Focal villitis	Group B β-haem.strep.

*Cultures from high vaginal swabs.

Adj.chor plate, Adjacent chorionic plate; β-haem.step , β-haemolytic steptococci.

(Schwartz *et al.* 1977), at 37°C for 2 h in an atmosphere of 95% O_2–5% CO_2. Hyperoxia may initially stimulate and then inhibit prostanoid production by placental tissue perfused *in vitro* (Kuhn *et al.* 1988), but under our conditions PGE production rates were constant over the 2-h incubation period. After incubation the tissue was recovered and dried to constant weight, and the medium used for PGE and lactate estimations (López Bernal *et al.* 1987*b*). Lactate was measured as an indicator of tissue viability. Under these conditions both PGE and lactate production rates were proportional to the dry weight of the tissue over the range 5–25 μg for amnion and choriodecidua and 20–50 μg for placenta (Spearman correlation coefficients 0·75–0·78; $P<0{\cdot}001$, $n = 20$ for each tissue). PGE and lactic acid were estimated without knowledge of the histology.

Statistical analyses

Statistical differences were assessed by the Kruskal–Wallis and the Mann–Whitney tests. Results are given as median and range.

Results

In preterm delivery associated with chorioamnionitis (group B) the gestational age was significantly shorter ($P<0{\cdot}001$) than in uncomplicated preterm labour (group A). Other clinical differences are shown in Table 1. The histological findings in the patients in group B are shown in Table 2. The most common type of inflammatory change was chorioamnionitis with funisitis, suggesting intrauterine infection; these patients were delivered very early in gestation. Other changes included chronic deciduitis and focal villitis of unknown aetiology. It is of particular interest that 4 of 7 patients with the most severe form of intrauterine inflammatory change, chorioamnionitis–funisitis, started labour with intact membranes. In some patients data from high vaginal swabs were available (Table 2). Placentas in the elective preterm delivery group (group C) showed changes typical of pre-eclampsia, but revealed no evidence of inflammation. In all the patients delivered at term, histology was normal.

PGE and lactate production by each tissue

When these values were analysed in tissues with normal histology, the highest PGE production rate (fmol/mg dry weight/2 h) was by amnion: 1763 (164–15 580) (median and range, $n = 92$), followed by placenta: 609 (150–3846, $n = 80$), and then by choriodecidua: 329 (39–3245, $n = 88$) ($P<0\cdot001$). There was a significant correlation between PGE production by amnion and choriodecidua (correlation coefficient (r) 0·71, $n = 88$, $P<0\cdot001$); between choriodecidua and placenta ($r = 0\cdot38$, $n = 78$, $P = 0\cdot015$); and between amnion and placenta ($r = 0\cdot35$, $n = 80$, $P = 0\cdot03$). The significant relation between PGE production rate by these different tissues suggests either that systemic or intrauterine factors regulate PG synthesis, or that PGE could be produced in all these tissues by a common cell type, e.g. the tissue macrophage.

Lactate production (μmol/mg dry weight/2 h) was highest in choriodecidua: 237 (48–565, $n = 87$), followed by placenta: 159 (85–548, $n = 80$) and amnion: 99 (18–474, $n = 91$) ($P<0\cdot001$). There was a significant correlation between lactate production rates in the three tissues ($r = 0\cdot38$–$0\cdot57$, $P<0\cdot005$–$0\cdot001$).

PGE and lactate production in the different groups

In the absence of inflammatory infiltration, PGE production by all three tissues was highest after spontaneous labour at term (group E) and lowest after spontaneous uncomplicated preterm labour (group A; $P<0\cdot05$) (Table 3). Moreover, amnion and choriodecidua showing chorioamnionitis (group B) were associated with the highest PGE output ($P<0\cdot001$), but not placenta.

Figure 1 shows the relation between gestational age and amnion PGE production in spontaneous preterm labour. Preterm labour associated with chorioamnionitis clearly occurs much earlier in gestation than uncomplicated preterm labour, and is associated with much higher PGE production by amnion and choriodecidua (Table 3).

At term, PGE output in the three tissues was higher after spontaneous labour (group E) than at elective caesarean section (group D) and the differences were statistically significant in placenta and choriodecidua ($P<0\cdot05$), although not in amnion. Values for the three tissues in the uncomplicated preterm labour (group A) were very similar to those in women delivered electively preterm (group C).

In the three women with antepartum haemorrhage, the PGE production rates for amnion, choriodecidua and placenta ranged 1453–2565, 153–470, and 853–1393 fmol/mg dry weight/2 h, respectively, well within the range in group A. The early pregnancy placental samples were histologically normal in four of the five specimens obtained at termination and the PGE output was 656 (244–931) fmol/mg dry weight/2 h. In one instance there was evidence of focal villitis with

Table 3. Prostaglandin E production (fmol/mg dry weight/2 h) in the different groups*

	Group A ($n = 21$–24)	Group B ($n = 13$–18)	Group C ($n = 9$–10)	Group D ($n = 26$–30)	Group E ($n = 25$–28)	P value
Amnion	1414 (164–11 045)	12 278 (1799–82 617)	1449 (393–3571)	2478 (202–8052)	2640 (360–15 580)	<0·001
Choriodecidua	308 (39–1086)	1018 (216–11 768)	321 (92–470)	379 (62–1681)	677 (100–3245)	<0·01
Placenta	578 (150–1859)	616 (89–4131)	764 (156–3846)	583 (360–1550)	1200 (520–3022)	<0·05

Results are medians and ranges.
P values from Kruskal–Wallis test.
*See Table 1 and text for explanation of groups.

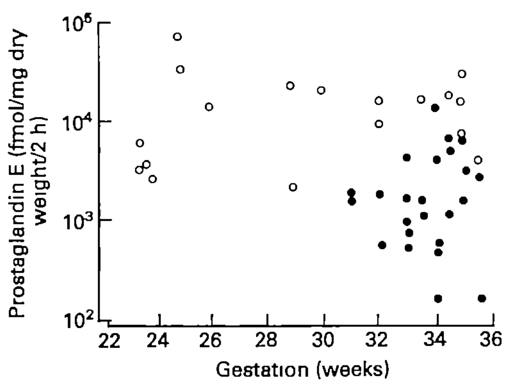

Fig. 1. Prostaglandin E production by amnion discs following spontaneous preterm labour. ●, Group A, normal placenta; ○, group B, inflammatory infiltration.

lymphocytic and plasma cell infiltration and PGE output was 117 000 fmol/mg dry weight/2 h. Lactate production rates were remarkably similar in all groups (Table 4).

Discussion

This study confirms that inflammatory infiltration of the placenta or fetal membranes is associated with extremely high PGE output by the amniotic epithelium (López Bernal *et al.* 1987*a*), and demonstrates a similar response by choriodecidual tissue showing inflammatory changes. Placental tissue did not show an unusually high PGE output in the chorioamnionitis group, perhaps because the inflammatory changes mainly affected the fetal membranes. Of course any increase in placental PGE production could be masked by the high placental PG dehydrogenase activity (Keirse 1979). Nevertheless, the huge PGE levels found in the early pregnancy chorionic villi suggest that at least in the first trimester the placenta responds to inflammation by increasing PG output. Some miscarriages may be due to this mechanism.

Preterm labour associated with chorioamnionitis could result from the high output of PGE by intrauterine tissues, for this would stimulate uterine contractility. Furthermore, many of the chemical mediators released in inflammatory reactions, such as histamine, bradykinin, serotonin and platelet-activating factor (PAF), provoke myometrial contractions (Tetta *et al.* 1986). Other compounds associated with local infection, including leukotriene B_4 and PAF, possess strong chemotactic properties which would amplify the inflammatory response. Leukotriene B_4 release is very high in fetal membranes showing leucocytic infiltration (López Bernal *et al.* 1987*a*) and the placenta shows a similar response (A. López Bernal *et al.*, in preparation). It seems possible that mediators of inflammation in intrauterine tissues, such as a placental leukotriene metabolite, could be detected and measured in the maternal circulation and serve as a specific marker of chorioamnionitis.

Bacterial products increase the production of PGE by human amnion cells (Lamont *et al* 1985; Romero *et al.* 1988), and some pathogenic bacteria have phospholipase activity that increases the availability of arachidonate for eicosanoid synthesis (Bejar *et al.* 1981; Bennett *et al.* 1988). Infiltrated amnion and choriodecidua respond to free arachidonate with a further increment in PGE production, so that in chorioamnionitis there is a large increase in PG synthetase activity (López Bernal *et al.* 1988). However, other eicosanoid pathways may also be activated because in the amniotic fluid of women with intrauterine infections there are raised levels of PGs and lipoxygenase products (Romero *et al.* 1987).

Table 4. Lactate production (μmol/mg dry weight/2 h) in the different groups*

	Group A (n = 19–24)	Group B (n = 15–18)	Group C (n = 9–10)	Group D (n = 25–30)	Group E (n = 23–28)	P value
Amnion	98(18–380)	102(18–474)	111(29–204)	99(47–152)	66(20–150)	NS
Choriodecidua	207(48–432)	225(118–565)	304(217–358)	265(185–347)	253(86–312)	NS
Placenta	157(86–267)	194(99–548)	178(97–226)	143(85–176)	145(106–185)	NS

Results are medians and ranges.
P values from Kruskal–Wallis test. NS, Not significant, P>0·05.
*See Table 1 and text for explanation of groups.

The striking difference in gestational age between the complicated preterm labour with chorioamnionitis and uncomplicated preterm labours with healthy membranes helps to explain the much poorer neonatal outcome in the former (Turnbull & López Bernal 1985; Lamont *et al.* 1986; Hillier *et al.* 1988). This difference in gestational age is often omitted when perinatal mortality rates in different preterm labour groups are quoted. While the prevention of preterm labour complicated by chorioamnionitis would considerably improve perinatal mortality, stopping preterm labour in this group would require aggressive management with a combination of drugs (McGregor 1988). Potent and safe anti-inflammatory drugs and antibiotics will need to be tested in controlled clinical trials. The use of PG synthesis inhibitors such as sodium meclofenamate with additional inhibitory effect on the myometrial PGE receptor may be considered (Rees *et al.* 1988). We have drawn attention previously to the potential risk of such drugs causing intrauterine closure of the ductus arteriosus (Sellers *et al.* 1981*a*) leading to persistent neonatal pulmonary hypertension if preterm labour does occur, but these risks may have been overemphasized (Amy *et al.* 1982). Rapid and accurate tests for the early diagnosis of chorioamnionitis in women admitted in preterm labour need to be developed.

Different approaches indicate that uncomplicated preterm labour starts and progresses with relatively low intrauterine PG release (Sellers *et al.* 1981*b*; López Bernal *et al.* 1987*a*; Kragt *et al.* 1988). The PGE values in group A were significantly lower than in group E, and patients in groups A and C had almost identical PGE production rates, despite the fact that in group A labour had started spontaneously whereas patients in group C were not in labour. This suggests that idiopathic preterm labour is not associated with increased intrauterine PG release. It could be argued that pre-eclampsia might have affected the results, but this was the only available elective preterm delivery group. Moreover, although the number of patients is small, our results indicate that preterm labour following severe antepartum haemorrhage and placental abruption with no inflammatory reaction is not associated with increased PG release by the placenta or fetal membranes.

The increase in placental and choriodecidual PGE production in group E compared with group D implies that these tissues, whose mass is considerable, may contribute to the raised circulating PG metabolites detected in women during spontaneous labour at term (Keirse 1979; Davidson *et al.* 1987).

The prevention of preterm labour remains a major aim of modern obstetrics. In uncomplicated preterm labour more research is necessary on myometrial function to define a possible increased sensitivity to endogenous agonists such as oxytocin (Takahashi *et al.* 1980; Fuchs *et al.* 1984). The prevention of preterm labour complicated with chorioamnionitis will be difficult because many of the predisposing socio-economic and medical factors are beyond the control of the obstetrician, but research in this area should have a great impact on perinatal mortality and morbidity.

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Changes in fetal monitoring practice in the UK: 1977–1984

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Summary. A postal survey was undertaken between 1985 and 1987 to assess the changes that have taken place in fetal monitoring practice since 1977. Replies were received from 253 (92%) of 276 consultant obstetric units canvassed. Biophysical methods of assessing fetal well-being in the antepartum period are almost universally employed and are accepted as the best discriminators of the need to deliver the pregnancy. The number of fetal heart rate monitors on labour wards has increased by 88%. Overall, 63% of units monitor more than 60% of their patients in labour, and 87% permit suitably trained midwives to apply fetal scalp electrodes, which must now be regarded as standard practice. There is still a need for a simplified technique for fetal blood sampling. The perinatal mortality rate correlates with a *prematurity factor* and probably bears a greater relation to the population served than to the degree of monitoring provided.

In 1978 a postal survey of intrapartum fetal monitoring practice in the UK (Gillmer & Coombe 1979) received replies from 244 (92%) of the 264 units canvassed. The approximate percentage of patients monitored electronically during labour in these units displayed a bimodal frequency distribution with peaks at 20–30 and 80–90%. This was interpreted as reflecting a division of opinion about the need to monitor all or only 'high-risk' patients. At that time, however, nearly 25% of units were unable to monitor all their high-risk labours. Only half the units allowed midwives to apply fetal scalp electrodes, and only 40% used fetal blood pH estimation. It was suggested that there was a need (i) to improve monitoring facilities in many units, (ii) to increase midwife involvement in practical monitoring techniques, and (iii) to develop improved methods for fetal pH determination during labour.

At that time the techniques for continuous electronic fetal heart rate (FHR) monitoring and fetal blood pH measurement had both been available for approximately 10 years. The arguments about the place of these techniques have continued to the present time despite a great deal of careful research, in particular the well-known randomized controlled trials (Haverkamp *et al.* 1976; Renou *et al.* 1976; Kelso *et al.* 1978; Haverkamp *et al.* 1979; Wood *et al.* 1981; MacDonald *et al.* 1985; Neldam *et al.* 1986).

The aim of the present survey was to obtain up-to-date information, to assess the changes that have taken place and if possible to establish the extent of agreement between consultant obstetricians concerning the use of these techniques. An attempt has also been made to assess the efficacy of cardiotocographic monitoring and

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fetal blood sampling in labour as practised in the UK.

Subjects and methods

In September 1985 a postal questionnaire was sent to one consultant at each of 305 units in the UK. Of the 305 units on the original list 29 did not provide intrapartum obstetric care, leaving 276 maternity units available for study. Further postal requests for information were made in February and December 1986 and each outstanding unit was contacted by telephone in May 1986. The results were analysed in April 1987.

The questionnaire

All those questions asked in 1978 were repeated with the addition of the following:

(1) In general, is fetal blood sampling done to confirm the diagnosis of fetal distress in the second stage of labour?

(2) In general, is maternal blood sampling done with fetal blood sampling to help interpret the result?

(3) If there were a simpler technique for fetal blood sampling do you think it would be used more often?

(4) In approximately what percentage of cases is the condition of the newborn infant assessed by:
  (a) The Apgar score?
  (b) Umbilical cord blood analysis?
  (c) If umbilical cord blood analysis is done, what specimens are usually collected?

(5) What methods are used to assess fetal wellbeing before the onset of labour:
  (a) Daily fetal movement charts?
  (b) FHR monitoring?
  (c) Ultrasound scan—growth and size?
  (d) Biophysical profile?
  (e) Oestriols
    urinary?
    serum?
  (f) HPL?
  (g) Which of these techniques do you consider to be the most reliable means of diagnosing fetal distress and the need for urgent operative delivery before the onset of labour?

(6) The perinatal mortality rate, the numbers of stillbirths, and early neonatal deaths, the percentage of deliveries <37 weeks gestation and/or <2500 g birthweight?

All information was transferred to computer disc and analysed using the Oxstat programme. Analysis of variance and the unpaired t-test were used when comparing perinatal mortality rates, stillbirth rates and neonatal death rates. The Mann–Whitney U-test was used when comparing 'prematurity factors'.

Multiple linear regression analysis was used to study the effects on the perinatal mortality rate of: (1) the unit monitoring policy; (2) the approximate percentage of patients monitored in labour; (3) the use of fetal blood sampling in the first stage of labour; (4) the number of deliveries per unit per year; (5) the number of deliveries per monitor per unit; and (6) the prematurity factor (this consists of either the percentage of deliveries <37 weeks gestation, or the percentage of infants <2·5 kg birthweight, or the mean of these two values when both were reported.

National birth figures were obtained from the OPCS and its equivalents in Scotland and Northern Ireland.

Results

Response to the survey

The previous survey included data from 244 (92%) of the 264 units canvassed. Since then some additional units have opened, while others have closed or been amalgamated. In the present survey replies were received from 253 (92%) of the 276 consultant obstetric units canvassed. The geographical distribution is shown in Table 1. The total number of women delivered in 1984 in responding units was 611 812 (84% of all deliveries nationwide) compared with 480 837 (73% of all deliveries nationwide) recorded in the 1978 survey. The response from Scotland was particularly prompt and complete.

Fetal heart rate monitoring equipment

The total number of monitors reported in this survey was 1656 (average 6·55 monitors per unit) compared with 848 monitors (average 3·48 monitors per unit) in the previous survey. This represents an 88% increase in the number of monitors available. The numbers of each make are shown in Table 2 and are compared with the findings of the previous survey.

Table 1. Replies by region

Region	No. of units contacted	No. of replies (%)
Scotland	25	25 (100)
Ulster	17	17 (100)
Northern	19	19 (100)
Anglia	9	9 (100)
Oxford	9	9 (100)
North West Thames	19	19 (100)
Wessex	12	12 (100)
South Western	11	11 (100)
West Midlands	20	19 (95)
South East Thames	21	20 (95)
South West Thames	14	13 (93)
Merseyside	10	9 (90)
North Western	20	17 (85)
North East Thames	21	17 (81)
Wales	16	13 (81)
Trent	15	11 (73)
Yorkshire	18	13 (72)
Totals	276	253 (91·7)

The number of patients per monitor per unit

In the previous survey the ratio of the number of deliveries per fetal heart rate monitor per unit ranged from 172 to 2708. In the present survey the ratio ranged from 117 to 1127 deliveries per monitor (mean 407, SD 178). There were 13 units with more than 763 (mean + 2 SD) deliveries per monitor. Figure 1 compares these data with the results of the previous survey; 156 units (57%) felt that they had enough fetal heart rate monitors and 95 (34%) felt that they did not. These views showed a weak correlation with the ratio of the number of deliveries per monitor per unit ($r = 0{\cdot}288$, $P<0{\cdot}001$, $n = 250$, regression slope 53, Y intercept 315 deliveries per monitor per unit).

The approximate percentage of patients monitored

The bimodal distribution revealed by the previous survey has disappeared with only 47 units (19%) monitoring fewer than 40% of their patients, 47 units (19%) monitoring 40–60%, 60 units (24%) monitoring 60–80% and 98 units (39%) monitoring more than 80% of their patients. Figure 2 compares these results with those of the previous survey. There is a weak positive correlation between the number of deliveries per unit and the approximate percentage of patients monitored ($r = 0{\cdot}203$, $P = 0{\cdot}001$, $n = 251$, regression slope = 183, Y intercept = 1734·6).

Unit monitoring policies

In the previous survey 91 consultants (37·7%) stated that they aimed to monitor all their patients in labour and 150 (62%) monitored only high-risk patients. In response to the present survey 117 consultants (46%) stated that they planned to monitor all their patients, 100 (39%) aimed to monitor high-risk patients only, and 35 (14%) monitored all patients at some time during labour but only 'high-risk' patients continuously. One consultant answered that there was no monitoring policy in his unit.

In the previous survey 122 units (50%) taught midwives to apply fetal scalp electrodes, and a higher percentage of patients was monitored in these units. In this survey midwives applied fetal scalp electrodes in 219 units (87%).

Fetal blood sampling

In the 1978 survey, fetal blood pH estimation was used in 98 hospitals (40%), and 38 (16%) had a pH meter on, or adjacent to, the labour ward although this was not used for pH estimation. In this survey, 111 units (44%) used fetal blood sampling as a method of fetal assessment in the first stage of labour, and 28 units (11%) stated that it was also used in the second stage of labour. Nine units (4%) made a simultaneous assessment of a maternal sample to assist in the interpretation of the fetal results.

Of the 253 responding units 125 (49%) had pH

Table 2. Numbers and makes of fetal heart rate monitors of each make used in 253 maternity units in the UK, 1984

Make	1977 *n* (%)	1984 *n* (%)
Sonicaid	592 (69·8)	952 (57·4)
Hewlett Packard	229 (27·0)	567 (34·3)
Corometrics	12 (1·4)	83 (5·0)
Huntleigh		17 (1·0)
Devices	5 (0·6)	
Roche	3 (0·4)	3 (0·2)
Others	7 (0·8)	11 (0·7)
Not specified		23 (1·4)
Total	848 (100)	1656 (100)

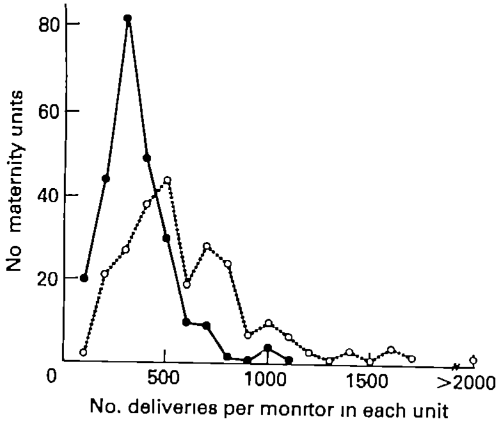

Fig. 1. Frequency distribution of the number of deliveries per monitor in maternity units in the UK in 1977 (O ·········· O) and 1984 (●——●)

measuring equipment on, or adjacent to, the labour ward (Table 3). Thus, 14 units (5%), although having the necessary equipment, did not use fetal blood pH estimation as a method of fetal assessment. Of the 235 responding consultants, 197 (84%) indicated that if there were a simpler technique for fetal blood sampling they thought it would be used more often; a further eight (3%) answered in the affirmative but with reservations. In no hospital did midwives perform fetal blood sampling.

Antenatal tests of fetal well-being

Details of antepartum fetal monitoring tests in use were requested in the current survey, and Table 4 shows the number of maternity units using each method.

Also included was a question to ascertain which of these tests is considered to be the most reliable indicator of fetal distress and the need for urgent operative delivery before the onset of labour. The question called for a single answer but, as indicated in Table 5, many consultants clearly felt that this was not possible. All those answering with more than two factors included fetal heart rate monitoring. When all those including this technique in their answer are added together the sum is 222 (89% of those responding). This figure excludes biophysical profile although in most cases this technique will include an assessment of the fetal heart rate.

Assessment of the newborn

Of the 250 consultants who responded to this question 246 (98%) indicated that >80% of newborn babies were assessed by the Apgar score. Sixteen units (6%) also used umbilical cord blood analysis in >20% of births, and 97 units (35%) reported using this technique on some occasions. Forty-one indicated that they took samples from the artery and vein, 28 sampled artery blood only, 27 vein blood only, and one stated that 'either the artery or the vein was sampled with no attempt to differentiate'.

Perinatal mortality statistics

Data reported about perinatal mortality are shown in Table 6. The total number of deliveries listed in Table 6 varies for each component of perinatal mortality because not every reply contained a complete set of information. It should be noted that calculating the 'mean rate per unit' gives the same weight to units with 500 deliveries that is given to units with 5000 and therefore is of doubtful value.

In this survey the number of deliveries per unit, the number of deliveries per monitor, the monitoring policy, the approximate percentage of patients monitored, and the use of fetal blood pH measurement in the first stage of labour were ascertained. Each of these data sets has been correlated with the perinatal mortality rate. The

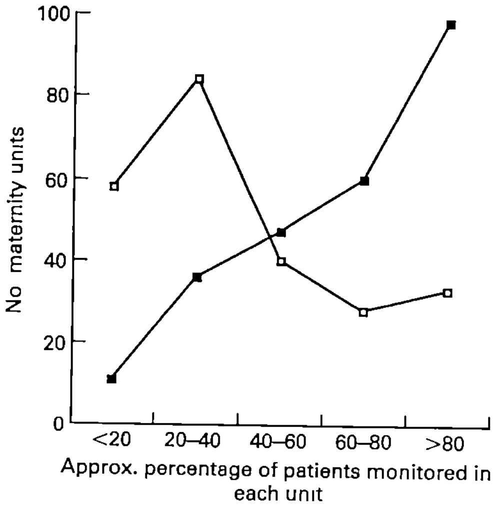

Fig. 2. Frequency distribution of the approximate percentage of patients monitored in each unit in 1977 (□) and 1984 (■)

Table 3. Type of pH measuring equipment used

Equipment	No. of units
pH meter (unspecified)	23
Radiometer	30
Corometric, Coromet 220 pH System	23
Instrumentation Laboratories	19
Corning	27
Others	3
Total	125

number of deliveries per unit and the approximate percentage of patients monitored showed weak positive correlations with the perinatal mortality rate. There were also positive correlations between the perinatal mortality rate and the percentage of deliveries at <37 weeks gestation and <2·5 kg birthweight, and with the 'prematurity factor' (Table 7).

However, when multiple linear regression analysis was performed with perinatal mortality rate as the dependent variable and including as independent variables the number of deliveries per year, the number of deliveries per monitor, the approximate percentage of patients monitored, the unit monitoring policy, the use of fetal blood sampling in the first stage of labour and the prematurity factor, only the prematurity factor was a significant influence ($P < 0{\cdot}02$).

The median prematurity factor for teaching hospitals plus those district general hospitals with more than 4000 deliveries per year is 7·5% (interquartile range 5·9–9·2%). The median prematurity factor for district general hospitals with ≤4000 deliveries per year is 5·9% (interquartile range 4·8–7·2%). There is a significant difference between these two sets of data ($P<0{\cdot}001$).

Discussion

This investigation was conducted in the same manner as the 1978 survey and the results depend on one consultant in each unit. The response to each survey was similar with approximately 92% of units replying to the questionnaire.

Availability of fetal heart rate monitoring equipment and unit monitoring policy

If labour on average is assumed to last 12 h and it is agreed that the fetal heart rate should be monitored continuously throughout labour, then it can be calculated that a minimum of one monitor is needed for every 730 deliveries per annum. This further assumes that labours are sequentially distributed in time, but since they occur randomly, more monitors would be required to be able to adopt such a policy. There has been an 88% increase in the number of monitors available and, as illustrated in Fig. 1, the range of the ratio, the number of deliveries per monitor per unit, has considerably reduced. There were, however, 13 units where this ratio was >763 (mean +2 SD).

Since 1978 a new approach to fetal monitoring has been introduced. Thirty-five consultants (14%) indicated that they plan to monitor all their patients for some period during labour but that continuous monitoring is used only in high-risk cases. In this situation fetal heart rate monitoring is being used as a test to identify high-risk cases in early labour. It is possible that this policy would have been selected much more frequently had it been a printed option on our questionnaire.

This survey did not reveal the same bimodal frequency distribution of the approximate percentage of patients monitored that was found in 1978. This statistic, however, is probably not recorded in many units and its accuracy may therefore be questioned. Furthermore, it is not clear how those units that adopt a policy of 'monitoring all patients at some time during labour' have answered this question. This may have contributed to the apparent disappearance of the bimodal frequency distribution.

The increase in the number of patients being monitored may be a reflection of the increased number of units (87%) where midwives apply fetal scalp electrodes. This statistic indicates that

Table 4. Methods of fetal monitoring before the onset of labour

Fetal monitoring	No. of units (n=253) n (%)
Fetal heart rate monitoring	251 (99·2)
Ultrasound: growth and size	251 (99·2)
Daily fetal movement charts	229 (90·5)
Biophysical profile	104 (41·1)
Oestriols	167 (66·0)
Urinary	75 (29·6)
Plasma	92 (36·4)
Human placental lactogen	82 (32·4)

Table 5. Antepartum test considered most reliable for diagnosing fetal distress before the onset of labour

	No. of units (*n*=253)
FHR monitoring	154
FHR + U/S biophysical profile	6
FHR + U/S growth and size	12
FHR + daily FM charts	5
Combination of >2 factors*	45
U/S biophysical profile	10
U/S growth and size	7
Daily FM charts	3
Urinary oestriol	3
Plasma oestriol	1
Placental lactogen	0
Others	4
No answer	3
Not returned	23
Total	276

* All included FHR monitoring.
FM, Fetal movement; FHR, fetal heart rate; U/S, ultrasound.

it is now standard practice for suitably trained midwives to apply fetal scalp electrodes and as such should be totally defensible in law. A survey in France by Blondel *et al.* (1989) showed that continuous electronic fetal heart rate monitoring was almost universally accepted by French obstetricians as an essential technique in every labour. Only 1% of the French responders used it only for high-risk patients. They quoted the principal reason for continuous monitoring as 'the early detection of fetal distress'. Other reasons given were the ability to carry out continuous surveillance without increasing the number of midwives, that 'nobody knows any longer how to look after women in labour without electronic monitoring' and 'women's demand'.

On four separate days in 1984 the National Birthday Trust carried out a survey into the facilities available at the place of birth (Chamberlain & Gunn 1987). This survey canvassed every institution in the UK where babies are born including all the units in our survey and also a large number of very small units largely staffed by general practitioners. They showed that 95% of units delivering between 501 and 2000 patients per year and 100% of those delivering more than 2000 women per year had equipment available for continuous electronic fetal heart rate monitoring. The large units (2001–4000 deliveries per year) showed the greatest variation in the number of deliveries per monitor available with 10% having more than 750 annual deliveries per monitor.

Fetal blood sampling

The value of fetal blood sampling as a method of fetal surveillance in labour would appear to remain controversial. There has been a small increase in the number and percentage of units employing this technique (from 40 to 44%) and there remain a few units (13, 5·5%) where the equipment is available but not used. Chamberlain & Gunn (1987) reported similar results, 31% of units delivering 2001–4000 patients per year, and 60% of those delivering >4000 women per year had access to fetal blood pH meters.

Gillmer & Coombe (1979) commented that there was a 'need for improved methods of fetal pH determination to be developed'. This would still appear to be the case since 87% of responding consultants felt that this investigation would be used more often if a simpler technique were available.

Antenatal tests of fetal well-being

Biophysical methods of fetal monitoring, including fetal heart rate monitoring, fetal movement charts, ultrasound measurement of fetal growth and size, and the biophysical profile, have

Table 6. Overall perinatal mortality

Mortality	No. of units	Total no. of deliveries	Mortality rate (per unit per 1000 total births) Mean (SD)
Perinatal deaths	249	605 523	9·91 (3·0)
Stillbirths	241	590 057	5·62 (2·0)
Early neonatal deaths	239	585 510	4·40 (2·1)

Table 7. Correlations with perinatal mortality rates

Variable	*n*	Correlation	*P*
No. deliveries per unit	249	0·209	<0·01
No. deliveries per monitor	249	0·094	NS
Unit monitoring policy	249	0·008	NS
Fetal blood sampling in first stage of labour	249	0·109	NS
Approximate percentage of patients monitored	248	0·151	<0·02
Percentage of deliveries			
<37 weeks gestation	133	0·233	<0·01
<2·5 kg birthweight	194	0·197	<0·01
Prematurity factor	206	0·181	<0·01

NS, Not significant.

become the standard methods of assessing fetal well-being. Blondel *et al.* (1989) reported that 99% of French obstetricians used ultrasound screening for every pregnancy. In women without any complications of pregnancy only 2% made a single ultrasound examination, 92% made two or three examinations, and 6% made four or more.

It is perhaps surprising that biochemical methods are still used to the extent indicated, since so few consultants regard them as reliable tests on which to base a decision to initiate delivery (Tables 4 & 5). Possibly the biochemical tests and daily fetal movement charts are used as screening procedures with subsequent recourse to more definitive biophysical methods where appropriate.

To ask clinicians to define one test as the most reliable means of determining fetal distress was perhaps unrealistic as it is almost always a situation where the whole clinical picture must be taken into consideration, hence the large number of answers indicating more than one test. The vast majority of responses included fetal heart rate monitoring.

Assessment of the newborn

Assessment of the newborn by the Apgar score is almost universal. It is well known that this score, originally designed as an *aide memoire* to those involved in resuscitation of the newborn, correlates poorly with the acid-base and blood gas status at birth (Sykes *et al.* 1982). The management of labour is directed towards the avoidance of the birth of an asphyxiated baby. Since it is relatively easy to measure the acid-base and blood gas status, if the necessary equipment is available, it would appear to be logical to perform such an audit of intrapartum care. However, the acquisition of additional data does not necessarily lead to a better outcome and the value of doing this as a routine has not been established.

Perinatal mortality statistics

An attempt was made to assess the influence on the perinatal mortality of (i) the unit fetal monitoring policy in labour, (ii) the approximate percentage of patients monitored in labour, and (iii) whether or not fetal blood sampling was carried out. No clear effect was demonstrated. The unit fetal monitoring policy and the use of fetal blood sampling in the first stage of labour bore no significant correlation to the perinatal mortality rate. There is a significant but weak positive correlation between the approximate percentage of patients monitored and the perinatal mortality rate, but multiple linear regression analysis, including other factors that might have an influence on the perinatal mortality rate, showed that only the prematurity factor maintained significance. Teaching hospital maternity units and the larger maternity units consistently deliver a greater percentage of high-risk pregnancies. This survey suggests that the perinatal mortality rate for each unit is predominantly affected by the number of preterm and low birthweight babies. The non-uniformity of the populations served by individual units means that no definite conclusions can be drawn from this survey about the efficacy of the fetal monitoring methods studied.

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Medroxyprogesterone acetate in the treatment of pelvic pain due to venous congestion

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Summary. Ovarian function was suppressed with 30 mg of medroxyprogesterone acetate, daily for 6 months, in 22 women with lower abdominal pain due to pelvic congestion. There was reduction in pelvic congestion demonstrated by venography in 17 of the 22 women, and in 16 this was associated with induction of amenorrhoea which suggests that effective ovarian suppression is an important component of successful treatment. In the 17 women who showed a reduction in venogram score, the median change in pain score was 75% compared with only 29% in the five women with no change in venogram score ($P<0{\cdot}01$). This significant association between reduction in pelvic congestion and pain indicates that pelvic congestion is likely to be the cause of pain in these women and that treatment with medroxyprogesterone acetate could be of value.

Over the years many investigators have suggested that dilatation of the pelvic veins associated with venous congestion is a common finding amongst women with no obvious cause for chronic pelvic pain (Taylor 1949; Hughes & Curtis 1962). Our results (Beard *et al.* 1984) confirmed the congestion and showed (Reginald *et al.* 1987) that specific venoconstrictors, such as dihydroergotamine, given intravenously during an acute attack of pain can relieve the congestion and the pain. The exact cause of the venous dilatation remains uncertain but indirect evidence suggests that it may be caused by an ovarian hormone(s). Pelvic pain and congestion are only observed during the reproductive years (Taylor 1949; Renaer *et al.* 1980); these women tend to have dysfunctional uterine bleeding (Beard *et al.* 1988) and have an enlarged uterus, thicker endometrium and, in 56%, polycystic changes of the ovaries are observed on ultrasound (Adams *et al.* 1986). In view of this evidence, it seemed reasonable to attempt to treat these women medically by suppressing ovarian function with a well-tolerated progestogen such as medroxyprogesterone acetate (MPA) (Provera) which is known to suppress ovulation and reduce circulating oestradiol to levels found in the early follicular phase of the cycle (Oritz *et al.* 1977; Mishell *et al.* 1972).

The object of the present study was to determine whether suppression of ovarian activity with MPA could improve the pain due to pelvic congestion.

Subjects and methods

The study included 22 women who attended the pelvic pain clinic consecutively complaining of

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chronic pelvic pain, for which no cause could be found at laparoscopy, and with venographic evidence of pelvic congestion (Beard *et al.* 1984). Their median age was 31 years (range 22–42), 18 of them were parous and four nulliparous. They were prescribed 30 mg of oral MPA (Provera, Upjohn) daily for 6 months. They were asked to keep a history of vaginal bleeding during this time and whether at any time during the treatment period they defaulted in taking the drug. They were seen before starting treatment and again at 3 and 6 months later.

Visual analogue scale pain score

The women were asked to indicate the severity of their pain on a visual analogue scale (VAS), before starting treatment and 3 and 6 months later, when treatment finished. This was later quantified on a 10 cm scale. Huskisson (1974) reviewed this quantitative method of describing pain and concluded that it was both sensitive and reproducible. The VAS pain score ranged from 0 to 10 with 0 indicating no pain and 10 unbearable pain.

Pelvic venography

Each woman had pelvic venography before the start of treatment and again at the end of treatment 6 months later. The technique and the methods of assessing the films were the same as those described previously by Beard *et al.* (1984). The films taken immediately after the injection of the dye into the uterine fundus, 20 and 40 s later, were scored to determine the severity of pelvic congestion. The venogram score takes into account three factors: the dilatation of the ovarian vein, the clearance time of dye, and a subjective assessment of the venous congestion of the ovarian plexus. The score can range from 3 to 9, values of 3 and 4 being within normal limits and values of 5 to 9 indicating pelvic congestion of increasing severity. The investigation was not correlated with a particular time of the cycle because the venogram score is not significantly affected by the day of the cycle in women with pelvic congestion (Reginald 1989).

Ultrasound scanning

This was done in all women in the study by one of the authors (J.A.) who had no knowledge of the results of other investigations. An Aloka sector scanner (SSD 720) with a 3·5 MHz long focused transducer was used. The ovaries were measured in three planes and the volume calculated (Sample *et al.* 1977). The same ovary was used for measurements before and after treatment. The uterine cross-sectional area was calculated from the product of measurements of the length from fundus to the cervix and the maximum depth (Adams *et al.* 1985). The endometrial echo was identified (Fleischer *et al.* 1986) and the thickness of the endometrium was measured at the maximum depth of the uterus.

Blood pressure and body-weight were recorded for all subjects at each visit.

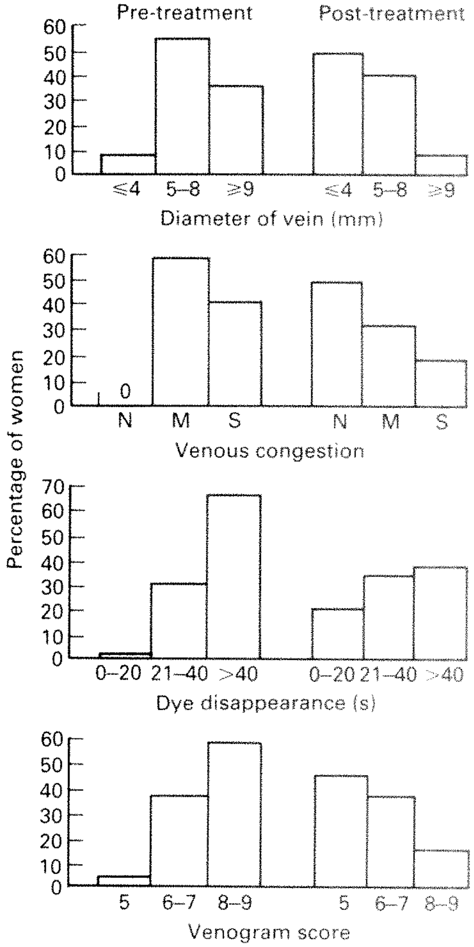

Fig. 1. Distribution of the composite venogram score and the three components of the venogram score before and after 6 months of treatment with medroxyprogesterone acetate. N, Normal; M, moderate; S, severe.

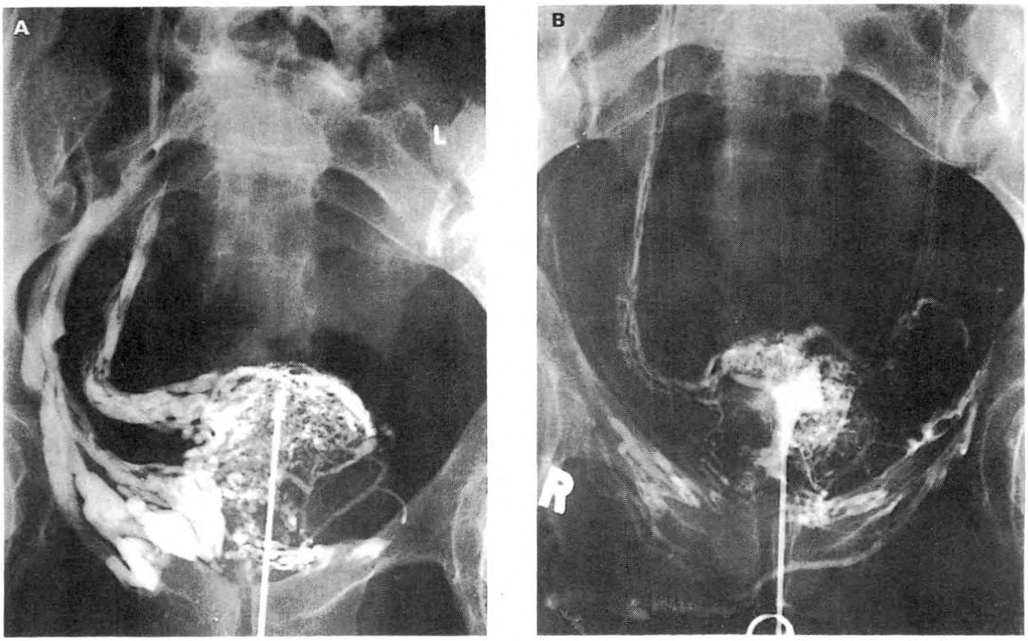

Fig. 2. Examples of venograms taken at the end of injection of the dye in a woman (A) before and (B) after 6 months of treatment with medroxyprogesterone acetate.

Statistical analysis

All statistical analyses used non-parametric methods as many of the within-subject differences before and after treatment were not normally distributed. The Wilcoxon matched-pairs signed rank test was used.

Results

Changes in the VAS pain score

All women showed a reduction in pain during treatment from a median pain score of 8·5 (range 7–10) to 4 (range 0–8) by the end of 3 months and to 2 (range 0–7) after 6 months of treatment. The reductions, both at 3 and 6 months, were highly significant ($P<0\cdot001$).

Pelvic venography

Figure 1 shows the distribution of the venogram scores before and after treatment. Before treatment the median score was 8 (range 5–9), which reduced to 5 (range 3–9) after treatment. This reduction is statistically significant ($P<0\cdot01$). Figure 1 also shows that treatment resulted in a reduction in all three variables from which the venogram score is derived. The reduction in pelvic congestion, presumably due to the reduced diameter of the pelvic veins and the improved blood flow through the pelvis, is striking. An example of the reduction in pelvic congestion before and after treatment is shown in Figs 2A and 2B.

Relation between venogram score, VAS pain score and amenorrhoea

Figure 3 shows the association between the venogram score and pain score. In the 17 women who had a reduction in the venogram score after treatment, the median percentage reduction in pain score was 75% compared with a median reduction of 29% in the five women who had no reduction in the venogram score ($P<0\cdot01$). Of these five women, the three who showed the least reduction in pain score continued to bleed vaginally during the 6 months of treatment whereas of the 17 women with marked improvement, 16 became amenorrhoeic during treatment.

Ultrasound findings

After treatment, 18 of the 22 women showed a reduction in the uterine area. The median uterine area was 39 cm^2 (range 26–60) before treat-

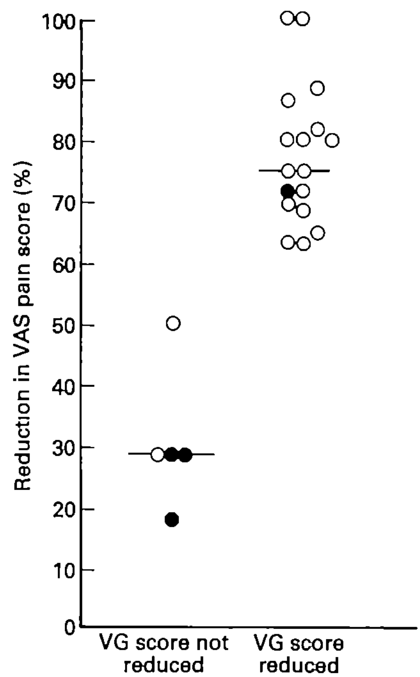

Fig. 3. Percentage reduction in visual analogue scale (VAS) pain score in 22 women grouped by reduction in venogram (VG) score after 6 months treatment with medroxyprogesterone acetate. ○, Women with amenorrhoea; ●, women with vaginal bleeding. The median value is indicated by the horizontal line.

ment which reduced to 31 cm^2 (range 17–53) after treatment ($P<0\cdot001$).

Endometrial thickness decreased in 18 of the 22 women showing a significant ($P<0\cdot001$) reduction from a median value of 10 mm (range 5–17 mm) before treatment to 6 mm (2–17 mm) after treatment.

Ovarian volume measurements were available for 21 women and 16 of them showed a reduction. The median volume was 9 ml (range 5–19) before treatment which reduced to 8 ml (range 3–18) after treatment ($P<0\cdot001$).

Overall, 13 women showed reduction in uterine area, ovarian volume and endometrial thickness, five women showed reduction in two of these measures, and three showed reduction in one.

Systemic effects of treatment with MPA

Before treatment the median body-weight of the women was 61 kg (range 40–74). There was a significant ($P<0\cdot001$) increase in median body-weight of 1 kg (range 0–4·9) at 3 months during treatment and of 3 kg (range 0·4–8) by the end of 6 months. There was no significant change in the mean arterial blood pressure.

Discussion

The results of this study show that treatment with MPA in women with demonstrable pelvic congestion leads to narrowing of the veins and a reduction in pelvic congestion presumably due to improved venous clearance. There was an associated reduction in pelvic pain which agrees with our previous findings (Reginald *et al.* 1987) in women with pelvic pain due to venous congestion who were treated with dihydroergotamine. The results also add in a small way to the very limited understanding as to why women develop pelvic congestion. We have hypothesized that ovarian dysfunction is in some way linked to pelvic congestion and for this reason have used MPA to suppress ovarian function. The fact that the pain and venogram scores improved most in women who became amenorrhoeic on treatment supports this view. However, it is paradoxical that MPA, the effects of which are similar to progesterone, can produce narrowing of the pelvic veins when it is generally believed that progesterone induces venous dilatation. A search of the literature reveals that there is no good basis for the belief that progesterone induces venous dilatation. McCausland *et al.* (1961) suggested, on unconvincing evidence, that progesterone is a venous dilator because of the parallel increase in venous distensibility and the serum concentration of progesterone with advancing pregnancy. Our studies on selective dilatation of the ovarian vein on the side of the developing ovarian follicle (Reginald *et al.* 1986) show that venous dilatation starts in the follicular phase and is maximal around the time of ovulation, that is, well before the local concentration of progesterone starts to increase in the vein. This suggests that oestrogen is a venous dilator and possibly has a more potent action than progesterone. This view is supported by the studies of Forbes & Glassen (1972) in mice. They showed that while oestrogen causes marked dilatation of ovarian and uterine veins, progesterone produced less dilatation and both dihydro- and hydroxyprogesterone produced no significant change. In one instance, 17-hydroxyprogesterone (of which Provera is a derivative) produced venous constriction. The studies of Greiss & Anderson

(1970) show that the vascular response to oestrogen is antagonized by progesterone.

MPA is a suitable progestogen for treating pelvic congestion because it is so well tolerated and safe even in large doses. However, because it only partially suppresses ovarian function, breakthrough bleeding is troublesome in a significant proportion of women (18%). In addition, our initial impression is that pelvic pain frequently returns when treatment is stopped. Nevertheless, the improvement these women experience whilst on treatment can reassure them that a correct diagnosis has been made. Psychological approaches have also been reported to be successful in the management of chronic pelvic pain (Pearce *et al.* 1982), and the effectiveness of treatment with MPA and psychotherapy has been assessed in a randomized controlled trial (Farquhar *et al.* 1989).

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A randomized controlled trial of medroxyprogesterone acetate and psychotherapy for the treatment of pelvic congestion

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Summary. The value of medroxyprogesterone acetate (MPA) and of psychotherapy in the treatment of lower abdominal pain due to pelvic congestion was assessed in a randomized controlled trial. Eighty-four women with abnormal pelvic venography were assigned to one of four treatment groups: MPA alone, MPA plus psychotherapy, placebo alone, and placebo plus psychotherapy. Women were treated for 4 months and thereafter followed up regularly for 9 months with pain assessments, pelvic ultrasound scanning, and hormone measurements. During treatment, MPA showed a significant benefit in terms of a reduction in visual analogue scale pain score, with 73% of women reporting at least 50% improvement compared with 33% of those treated with placebo. At 9 months after the end of therapy there was no overall significant effect of MPA or psychotherapy, but there was an interaction between MPA and psychotherapy, with 71% of the women in this group showing a ≥50% reduction in pain score. Therapy with MPA is a useful first-line therapy for women with pain associated with demonstrable pelvic congestion.

Chronic lower abdominal pain without obvious pathology is a common symptom in women during the reproductive years. Our findings suggest that in many of these women a state of chronic pelvic venous dilatation leads to congestion which worsens under certain conditions, resulting in pelvic pain (Beard *et al.* 1984, 1988; Reginald *et al.* 1987). Despite a large literature on the subject extending over at least 150 years, no effective treatment has been found, so that many gynaecologists have resorted to hysterectomy which is obviously not desirable in a group of such young women.

With the advent of laparoscopy, pelvic venography and ultrasound scanning, the aetiology of the condition has become clearer. Taylor (1957) noted that these women often had an enlarged uterus and cystic ovaries. In agreement with these findings our studies (unpublished observations) have shown a 56% prevalence of polycystic ovaries on ultrasound scanning with an increase in uterine area and thicker endometrium than normal which suggests that

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ovarian hormones may be implicated in producing pelvic congestion.

Suppression of ovarian function might therefore be expected to produce relief of pain by reducing pelvic congestion. Medroxyprogesterone acetate (MPA) has been chosen for this purpose because it is well tolerated without many of the unpleasant androgenic and antioestrogenic side-effects of other agents. In a pilot study, 22 women with pelvic congestion demonstrated by venography were treated with 30 mg MPA daily for 6 months (Reginald *et al.* 1989). At the end of treatment, 18 women had a significant reduction in pain with a reduction in venous congestion seen on venography. Psychotherapy has also been shown to reduce the frequency and the severity of pain in women with unexplained pelvic pain (Pearce *et al.* 1982; Pearce 1986).

These preliminary results of two very different approaches to the treatment of pain due to pelvic congestion need to be tested in a randomized controlled trial. The aim of this study was to determine the effectiveness of MPA and psychotherapy, both individually and in combination, in reducing the pain of pelvic congestion.

Patients and methods

Study design

The study was designed to assess the effect of two different treatments, MPA and psychotherapy, and therefore four treatment groups were required: MPA alone, MPA and psychotherapy, placebo alone, placebo and psychotherapy. To have 90% power to detect as significant at the 5% level a difference in improvement of pain of 40%, 21 patients were required in each of the four groups. It was expected that 30% of women given placebo would show an improvement in pain and it was considered to be a clinically significant effect if 70% of the women on active treatment showed an improvement in pain.

After initial assessment by history, laparoscopy, and venography, 102 women were randomized between four groups: group 1, MPA only (25); group 2, MPA and psychotherapy (26); group 3, placebo tablets alone (25); and group 4, placebo tablets and psychotherapy (26). All women were treated for 4 months and followed up at the clinic for a further 9 months after the end of therapy. Approval for the study was obtained from St Mary's Hospital ethics committee.

Selection of women

Women were eligible to enter the trial if they had a history of pelvic pain for at least 6 months, no obvious pathology on laparoscopy, and a venogram score of $\geqslant 5$ which is indicative of pelvic congestion (Beard *et al.* 1984). The venogram score is a composite of scores for ovarian vein dilatation, venous congestion and clearance time of dye. Each factor is given an individual score from 1 to 3 so that a summated score of 3 indicates a normal venogram and a score of 9 is evidence of severe pelvic congestion. Any woman with a recent history of psychiatric illness or a history of thromboembolic disease was excluded. All women entering the trial gave written consent.

Figure 1 shows the distribution of the 200 women originally considered before randomization for entry into the trial; 34 of them were not suitable for investigation (12 had had hysterectomies, seven were postmenopausal and 15 declined the venogram or laparoscopy). Of the other 166 women who had venography, 50 were not eligible for the study for the following reasons: 21 had normal venograms and no pathology, 15 had pathology (endometriosis in five and pelvic inflammatory disease in 10) and 14 did not meet the entry criteria. Of the remaining 116 women who met all entry criteria 14 declined (nine were unwilling and five wanted to conceive). Of the women with a normal pelvis at laparoscopy 81% had abnormal venograms compared with 84% in a series reported by Beard *et al.* (1984).

Randomization and treatment

Randomization was achieved by giving each woman a numbered box which contained either 50-mg capsules of MPA or matching placebo identical in appearance to the MPA capsules. The boxes were supplied and numbered by the manufacturers (Upjohn Ltd) in such a way that each batch of four boxes contained two MPA and two placebo boxes in random order. The sequence was known only to the manufacturers and the statistician (J.W.). The numbers were then further subdivided so that there were three members of each of the four groups (MPA only, MPA and psychotherapy, placebo only, placebo

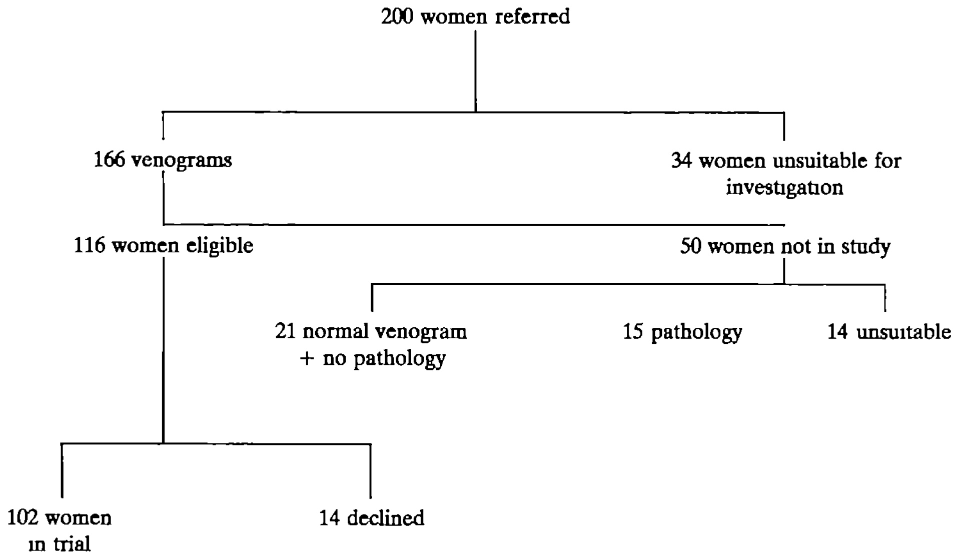

Fig. 1. Distribution of women attending pelvic pain clinic who were originally considered for entry to the trial.

and psychotherapy) in random order in every 12 numbers. The numbers were then sealed in envelopes and given to the research sister (V.R.) who allocated each woman to the appropriate group. This ensured that the drug allocation was double blind and the allocation of psychotherapy was random. The code was only broken at the end of the trial period.

It was recognized that the women might know whether or not they were receiving MPA because of the effect on their menstrual cycle. Therefore they were all told that both treatments, MPA or placebo, could induce amenorrhoea, irregular vaginal bleeding or have no obvious effect. In addition, women were asked to stop all forms of hormonal or intrauterine contraception and to use barrier methods throughout the 13 months of the trial.

Women allocated to the psychotherapy groups were asked to attend for six sessions, each 45 min in length, held at approximately fortnightly intervals. The therapy was an amalgamation of the effective ingredients of two psychological approaches to pain management incorporating graded exercise programmes with a behavioural analysis of pain episodes and the relation of pain to environmental stresses (Pearce 1986). The women kept detailed records of pain episodes and associated cognitive and behavioural responses to pain. The aim of treatment was to teach positive coping strategies and to increase activity levels. Treatment manuals were followed to ensure similarity of treatment across subjects and therapists.

Indices of outcome

Visual analogue scale pain score. Measuring the severity of pain using a visual analogue scale (VAS) is a well-validated method (Huskisson 1974). Women were asked to score on a 10-cm scale the average intensity of pain for the previous month at the first and at each subsequent visit. A successful outcome of treatment was defined as a ≥50% reduction in the VAS score from the score recorded before the start of treatment.

Pain improvement rating scale. At each visit women were asked if their pain was improved, unchanged or worse.

Follow-up appointments were scheduled at the end of 1 (S+1), 3 (S+3) and 4 (S+4) months of therapy. Thereafter they were at 3 (S+7), 6 (S+10) and 9 (S+13) months after the end of therapy. At each visit pain scores were recorded by the research sister (V.R.) and side-effects from treatment were recorded by the doctor (C.F.) to reduce any bias of pain scoring. Vaginal smears were taken at the pretherapy visit and at the end of therapy to estimate the karyopyknotic index (KPI) which is the percentage of superficial squamous cells with pyknotic nuclei, excluding parabasal cells, in a vaginal smear. Blood samples were collected for oestradiol, testosterone, progesterone (end of therapy visit only) and gonadotrophins at the pretherapy and end of therapy visit. Samples for MPA levels were collected at all but the last two visits. Hormone levels were standardized at the pretherapy visit by collecting blood from all women between cycle days 5 and 9. No attempt was made to standardize sample collection subsequently because of the interference with cycle resulting from treatment. Methods used for hormone assay were as described by Adams *et al.* (1985). Ultrasound scans were performed to measure the uterine area and the endometrial thickness before the start of treatment and 4, 7 and 13 months later. The methods of measurement have been described by Adams *et al.* (1988). Uterine cross-sectional area is a product of the maximum depth and of the length of the uterus in longitudinal view.

Statistical analysis of data

MPA levels were not normally distributed and are therefore presented as medians and ranges. Other data that were not normally distributed were transformed either by logarithm (oestradiol and progesterone) or square root (KPI, uterine area and gonadotrophins) before analysis. The results are presented in appropriate units. Dichotomous variables were analysed using log-linear models thus taking into account MPA and psychotherapy simultaneously and they are presented as percentages. Continuously distributed variables such as weight were analysed using analysis of variance and the results are presented as means and the interval one standard deviation above and below the mean. In both log-linear models and analysis of variance, interactions between MPA and psychotherapy were included and assessed.

Results

Of the 102 women included in the trial after randomization, 84 completed the full 13 months of the study. Of the other 18 women, 12 withdrew during the treatment period, and a further six during the follow-up period. Reasons for withdrawing during therapy were failure to attend the clinic (6), pregnancy (2) (on placebo tablets), dissatisfaction with treatment (2), and inability to maintain the trial protocol (2). Reasons for withdrawing during the follow-up period were pregnancy (4), failure to attend (1) and major surgery (1). The withdrawals were evenly distributed between the four groups; at the end of therapy the numbers of women in groups 1, 2, 3 and 4 were, respectively, 23, 22, 21 and 24, and at the end of the 9-month follow-up period the corresponding numbers were 23, 21, 19 and 21.

Characteristics of women and treatment compliance

At the start of treatment, the groups were comparable for age, parity, pain and venogram scores (Table 1). The duration of pain varied from 27 to 60 months; 82% of all women were Caucasian. There were no statistically significant differences between the groups.

Compliance with treatment with MPA was assessed by measuring serum MPA in 80 of the

Table 1. Details of the patients and their pain by treatment group

	Treatment group*				
	1 MPA only (*n*=25)	2. MPA + Pt (*n*=26)	3. Placebo only (*n*=25)	4. Placebo + Pt (*n*=26)	Total (*n*=102)
Age (years) Mean (SD)	29·4 (5·4)	27·9 (5·8)	30·1 (5·4)	31·8 (5·9)	29·8 (5·6)
Nulliparous *n* (%)	9 (36%)	17 (65%)	10 (40%)	7 (28%)	53 (52%)
Duration of pain (months)					
Median (range)	49·0 (6–300)	27·0 (6–120)	42·0 (12–180)	60·0 (6–180)	44·5 (6–300)
VAS pain score					
Median (range)	8·0 (4·0–10·0)	8·0 (4·0–10·0)	9·0 (6·0–10·0)	8·5 (4·0–10·0)	8·0 (4·0–10·0)
Venogram score Mean (SD)	6·5 (1·1)	6·5 (0·8)	6·5 (1·0)	6·7 (0·9)	6·6 (0·9)

*MPA, Medroxyprogesterone acetate; Pt, psychotherapy.
VAS, Visual analogue scale.

Table 2. Medroxyprogesterone acetate levels (MPA) in the four treatment groups

	MPA (ng/ml) in treatment group			
Time of sampling‡	1. MPA only	2. MPA + Pt	3. Placebo only	4. Placebo + Pt
Start of therapy(S)	0·0 (0–0) (n=14)	0·0 (0–1·0) (n=18)	0·0 (0–0) (n=18)	0·0 (0–0) (n=14)
S + 1	18·9 (12·9–51·8) (n=19)	24·0 (12·8–63·3) (n=20)	0·0 (0·0–2·2) (n=19)	0·0 (0·0–2·0) (n=19)
S + 3	28·5 (4·4–96·4) (n=18)	24 9 (0 0*–62·6) (n=19)	0·0 (0·0–1·2) (n=17)	0·0 (0·0–1·7) (n=15)
S + 4	16·4 (0·0†–59·3) (n=18)	19·3 (0·0†–51·8) (n=20)	0·0 (0·0–1·3) (n=19)	0·0 (0·0–2·0) (n=23)
S + 7	0·0 (0·0–1·4) (n=16)	0·0 (0·0–4·1) (n=20)	0·0 (0·0–0·0) (n=13)	0·0 (0·0–0·0) (n=14)

Results show the median (range) and n indicates the number of patients.
MPA, Medroxyprogesterone acetate; Pt, psychotherapy.
* Non-compliant patient.
† Two patients attended after finishing the tablets.
‡ S + 1, S + 3 and S + 4 indicate 1, 3 and 4 months, respectively, after the start of therapy, S + 7 indicates 3 months after end of therapy.

90 women who completed the 4 months of treatment (in 10 samples insufficient serum was available). Table 2 shows that overall compliance was excellent. One woman had an undetectable level after 3 months treatment indicating that she had not taken the tablets shortly before the sample was collected, but 1 month later her MPA levels were within the expected range, demonstrating that she was taking the tablets again. Four of the women in groups 1 and 2 had undetectable levels at the end of treatment because they had finished the course of tablets shortly before attending for follow-up.

Attendance at psychotherapy was variable with a mean attendance of 4·8 sessions out of a maximum of six for groups 2 and 4.

VAS pain score (Table 3)

After 3 months of treatment a 50% reduction in the VAS pain score was noted in significantly more women in the two MPA-treated groups (58%) compared with the placebo groups (28%) (P<0·01). At the end of treatment there was a more pronounced effect of MPA with 73% of the two MPA groups recording a 50% reduction in pain score compared with 33% of the two placebo groups (P<0·001). After stopping treatment, the pain returned in a proportion of the women in the MPA-treated groups whereas it remained unaltered in the placebo groups. Nine months after stopping treatment there was no overall significant effect of MPA or psychotherapy but there was a significant interaction (P<0·05) between MPA and psychotherapy with 71% of the women in group 2 (MPA+psychotherapy) showing a 50% reduction in pain score compared with only 43% of those in group 1 (MPA only), 53% in group 3 (placebo alone), and 29% in group 4 (placebo plus psychotherapy).

Pain improvement rating scale (Table 4)

A similar pattern of response to treatment was observed using the pain improvement rating scale. After 4 months of treatment, 37 of 45 women (82%) in the two MPA-treated groups said they felt the pain was improved compared with 24 of 45 (53%) in the two placebo groups (P<0·01). This finding was maintained at 3 months after the end of therapy but 9 months after treatment ended there was no significant difference between the groups.

Influence of psychotherapy

The results in Tables 3 and 4 suggest that psychotherapy did not improve pain intensity significantly in the short term. However, there was a positive interaction between MPA and psychotherapy 9 months after stopping treatment. In addition, of the women receiving psychotherapy (groups 2 and 4) those who had an

Table 3. Proportion of women with a 50% reduction in visual analogue scale pain score (from visit no. 1) in the treatment groups at each visit

	Treatment groups*				
Time of visit†	1. MPA only	2. MPA + Pt	3 Placebo only	4. Placebo + Pt	
S + 1	9/22 (41%)	5/23 (22%)	4/22 (18%)	4/24 (17%)	NS
S + 3	14/23 (61%)	12/22 (55%)	3/19 (16%)	9/24 (37%)	$P<0\cdot01$[1]
S + 4	17/23 (74%)	16/22 (73%)	8/21 (38%)	7/24 (29%)	$P<0\cdot001$[1]
S + 7	9/21 (43%)	13/21 (62%)	8/20 (40%)	7/24 (29%)	NS
S + 10	10/20 (50%)	10/17 (59%)	8/18 (44%)	9/20 (45%)	NS
S + 13	10/23 (43%)	15/21 (71%)	10/19 (53%)	6/21 (29%)	$P<0\cdot05$[2]

[1] Significant for MPA effect; [2] significant interaction between MPA and psychotherapy. NS, Not significant.

* MPA, Medroxyprogesterone acetate; Pt, psychotherapy.

† S + 1, S + 3 and S + 4 indicate 1, 3 and 4 months, respectively, after the start of therapy, S + 7, S + 10 and S + 13 indicate 3, 6 and 9 months, respectively, after the end of therapy.

improvement in pain (≥50% reduction in VAS score) at the end of 4 months had attended more psychotherapy sessions (mean 5·3 visits) than those who did not improve (mean 4·3 visits) ($P<0\cdot001$).

Uterine area and endometrial thickness

Uterine size assessed by ultrasound measurement of cross-sectional area throughout the period of study is shown in Table 5. There was a significant reduction in uterine size in both MPA-treated groups at the end of 4 months of treatment ($P<0\cdot05$) which was not present 3 months later. At the end of the study there was no significant difference in the mean uterine area between the four groups.

A similar pattern of change was observed with endometrial thickness with a reduction in the MPA-treated groups from a mean of 8·9 mm (SD 3·0) before treatment to 5·8 mm (SD 2·9) at the end of treatment ($P<0\cdot001$). No significant change in mean thickness was observed in the placebo groups. By the end of the study, mean values for all groups were not significantly different from measurements at the start of the study.

Hormone studies

There was no statistically significant difference between groups in pretherapy hormone concentrations.

Oestradiol levels

The pretherapy mean (mean ± 1 SD) oestradiol level for all subjects was 130·6 pmol/l (50·3, 339·3) (taken on days 5 to 9 of the menstrual cycle). Oestradiol levels were significantly lower ($P<0\cdot001$) during therapy in the MPA-treated groups with mean (mean ± 1 SD) values of 117·8

Table 4. Proportion of women whose pain was improved on the patient improvement rating scale in the four treatment groups at each visit

	Treatment groups*				
Time of visit†	1 MPA only	2 MPA + Pt	3 Placebo only	4 Placebo + Pt	
S + 4	21/23 (91%)	16/22 (73%)	11/21 (52%)	13/24 (54%)	$P<0\cdot01$[1]
S + 7	9/17 (53%)	14/19 (74%)	6/17 (35%)	10/23 (43%)	$P<0\cdot05$[1]
S + 10	9/18 (50%)	10/17 (59%)	8/18 (44%)	5/15 (33%)	NS
S + 13	12/23 (52%)	10/21 (48%)	10/19 (53%)	6/21 (29%)	NS

[1] Significant for MPA effect.

* MPA, Medroxyprogesterone acetate; Pt, psychotherapy.

† S + 4 indicates 4 months after the start of therapy, S + 7, S + 10 and S + 13 indicate 3, 6 and 9 months, respectively, after the end of therapy.

Table 5. Uterine cross-sectional area (fibroids excluded) in the four treatment groups at each visit

Time of measurement[†]	Uterine cross-sectional area (cm^2) in treatment group[*] 1. MPA only	2. MPA + Pt	3 Placebo only	4. Placebo + Pt
Start of therapy	33·4 (25·2, 42·8) (n=23)	29·7 (21·9, 38·5) (n=24)	31·3 (23·4, 40·4) (n=21)	34·6 (26·3, 44·2) (n=24)
S + 4	28·4 (22·1, 35·5) (n=21)	26·7 (20·6, 33·5) (n=20)	31·5 (24·9, 38·9) (n=18)	34·1 (27·2, 41·7) (n=21)
S + 7	33·3 (24·4, 43·7) (n=21)	29·6 (21·2, 39·4) (n=19)	31·8 (23·1, 42·0) (n=16)	36·5 (27·1, 47·3) (n=21)
S + 13	33·4 (23·4, 45·2) (n=20)	30·8 (21·3, 42·1) (n=18)	30·6 (21·1, 41·9) (n=18)	35·2 (25·0, 47·3) (n=20)

Results are expressed as mean (mean ± 1 SD) using square root transformed data. There was a significant effect of MPA at 4 months after the start of therapy ($P<0{\cdot}05$).

[*] MPA, Medroxyprogesterone acetate; Pt, psychotherapy

[†] S + 4 indicates 4 months after the start of treatment, S + 7 and S + 13 indicate 3 and 9 months, respectively, after the end of treatment.

pmol/l (50·8, 272·7) in group 1 and 148·7 pmol/l (64·0, 344·1) in group 2 compared with values in the placebo groups of 288·1 pmol/l (124·4, 667·6) in group 3 and 311·0 pmol/l (134·3, 720·2) in group 4.

Karyopyknotic indices (KPI)

The pretherapy mean (mean ± 1 SD) KPI level for all subjects was 43·5% (18·5, 69·1). At the end of therapy KPI levels were significantly lower ($P<0{\cdot}01$) in groups 1 and 2 with values of 30·7% (11·2, 60·0) in group 1 and 15·7% (3·1, 38·0) in group 2 compared with values in the placebo groups of 40·5% (17·3, 73·4) in group 3 and 37·9% (15·6, 69·8) in group 4.

Gonadotrophin levels

The pretherapy mean (mean ± 1 SD) luteinizing hormone (LH) level was 5·4 mmol/l (2·2, 8·1) for all subjects (taken days 5 to 9 of the menstrual cycle). During therapy LH levels were significantly lower ($P<0{\cdot}05$) in the MPA-treated groups with mean (mean ± 1 SD) values of 3·9 mmol/l (0·5, 10·4) in group 1 and 3·6 mmol/l (0·4, 9·9) in group 2 compared with values in the placebo groups of 4·6 mmol/l (0·8, 11·5) in group 3 and 8·9 mmol/l (3·0, 17·9) in group 4. There were no significant differences in follicle-stimulating hormone levels from pretherapy levels during the study.

Testosterone levels

The pretherapy mean (SD) testosterone level was 1·7 mmol/l (0·6) for all subjects. At the end of therapy testosterone levels were significantly lowered ($P<0{\cdot}001$) in the MPA groups with mean (SD) values of 1·6 mmol/l (0·6) in group 1 and 1·4 mmol/l (0·6) in group 2, compared with the placebo groups with values of 1·8 mmol/l (0·6) in group 3 and 1·9 mmol/l (0·6) in group 4.

Progesterone

Pretherapy progesterone levels were not measured. At the end of therapy progesterone levels were significantly lower ($P<0{\cdot}001$) in the MPA-treated groups with mean (mean ± 1 SD) values of 1·2 mmol/l (0·7, 1·8) in group 1 and 1·3 mmol/l (0·7, 2·5) in group 2 compared with the women in placebo groups with values of 2·7 mmol/l (0·7, 10·3) in group 3 and 5·6 mmol/l (4·0, 7·9) in group 4. None of the MPA-treated women had a serum progesterone value within the ovulatory range.

Table 6. The proportion of women with side-effects in the four treatment groups at end of therapy

	Treatment group*				
	1. MPA only	2. MPA + Pt	3. Placebo only	4. Placebo + Pt	
Weight gain at end of therapy	21/23 (91%)	17/22 (74%)	6/18 (33%)	8/22 (36%)	$P<0\cdot001^1$
Amenorrhoea at end of therapy	12/23 (52%)	14/22 (64%)	0/21 (0%)	1/23 (4%)	$P<0\cdot001^1$
Headaches	9/23 (39%)	11/22 (50%)	7/21 (33%)	9/24 (38%)	NS
Decreased libido	7/23 (30%)	5/22 (23%)	4/21 (19%)	7/24 (29%)	NS
Bloating	15/23 (65%)	15/22 (65%)	9/21 (43%)	7/24 (29%)	$P<0\cdot01^1$
Hot flushes	9/23 (39%)	2/22 (9%)	5/21 (24%)	6/24 (25%)	NS
Nausea	3/23 (13%)	2/22 (9%)	3/21 (14%)	5/24 (21%)	NS
Vaginal dryness	1/23 (4%)	7/22 (32%)	3/21 (14%)	3/24 (12%)	NS

[1] Significant MPA effect

NS, Not significant.

* MPA, Medroxyprogesterone acetate; Pt, psychotherapy.

Menstrual cycles (Table 6)

Of the 45 women in the MPA groups, 26 (58%) became amenorrhoeic during therapy. In the other 19 women, bleeding was cyclical in 5 (26%) and varied from a brown discharge to light bleeding in 13 (68%). Only one woman experienced moderately heavy bleeding. The bleeding was not sufficiently troublesome to require any woman to withdraw from the study.

Side-effects (Table 6)

Of the 45 women receiving MPA, 38 (84%) had gained weight by the end of the treatment period as compared with 14 of 40 women in the placebo groups (35%) ($P<0\cdot001$). The mean (SD) weight gain in the MPA groups was 2·4 kg (2·8) in group 1 and 1·5 kg (2·8) in group 2 compared with values in the placebo groups of −1·2 kg (2·8) in group 3 and −0·7 kg (2·8) in group 4. This increase in weight persisted up to the end of the study.

The only other symptom that was significantly increased in the MPA-treated groups was bloating which was experienced by 65% compared with 36% in the placebo groups ($P<0\cdot01$). Headache, decreased libido, hot flushes, nausea and vaginal dryness were experienced to some degree in all groups, but were not significantly increased in the MPA-treated groups. There was no significant difference in systolic or diastolic blood pressure between the groups.

Discussion

This study has confirmed our preliminary conclusions (Reginald *et al.* 1989) that MPA therapy can reduce pain significantly in women with lower abdominal pain due to pelvic congestion. Once treatment ceases then the pain tends to return. The second conclusion is that up to 9 months after stopping treatment almost 50% reported improvement in pain irrespective of treatment. At this follow-up point, 9 months after MPA and psychotherapy has stopped, there is a significant improvement in women treated with MPA plus psychotherapy compared with those treated with MPA or placebo alone or placebo plus psychotherapy.

Improvement in pain at the end of therapy was registered both by the VAS pain score and the pain improvement rating scale. It is interesting to observe that pain improvement by the rating scale was maintained 3 months after the end of therapy but not by the VAS. One possible reason for this difference between measurements of pain outcomes may be the unreliability of the pain improvement rating scale when compared with the VAS. The unreliability may arise in part because the woman's general outlook is influencing the pain improvement rating.

The explanation for these findings is likely to be complex because of the known interaction between psychological and somatic factors in pain. On the somatic side the data support the hypothesis that pelvic congestion is in some way dependent on the effects of ovarian hormones. Treatment with MPA reduced circulating oestradiol levels and end organ response to oestrogens as shown by the lowered vaginal KPI and reduced uterine cross-sectional area. Once treatment ceased, the pain returned in some but not all women with a rise in oestradiol concentration and a return in uterine size and endometrial thickness to pretherapy values. These findings, in conjunction with our venographic studies which showed an improvement in pelvic congestion in MPA-treated women who become amenorrhoeic (Reginald *et al.* 1989), support the view that when congestion is present, it is the cause of pelvic pain (Reginald *et al.* 1987).

The strong placebo response and the lasting improvement in pain 9 months after stopping treatment, irrespective of treatment group, suggests psychological factors are also implicated in the pain improvement. In the present study, all women were able to seek additional contact with the research nurse (V.R.) and doctor (C.F.) responsible for the study, either by extra clinic visits or by telephone. Such ease of contact with clinic staff may have tended to mask the beneficial effects of psychotherapy. This would also partly explain our apparent failure to obtain more favourable short-term results with psychotherapy which were expected from the results obtained by Pearce (1986). It is not clear from our results whether or not significant long-term changes were being effected in women receiving psychotherapy in addition to MPA. It is possible that the short-term improvement in pain effected by MPA allows the woman to gain a sense of control over the pain which makes it easier for her to practise the coping strategies taught during psychotherapy which are thus learnt more effectively.

The mechanism of action by which MPA reduces the pain of pelvic congestion is not clear. MPA reduces ovarian oestrogen secretion by suppressing ovulation and follicular function as shown by the reduced serum oestradiol and KPI of vaginal cells. There may also be a direct progestogenic effect as judged by the KPI. In addition, there is a possibility that MPA acts by reducing the level of oestrogen receptors in the uterus (Tseng & Gurpide 1975).

Side-effects from the use of a relatively high dose of MPA have been few Persisting weight gain, although small, is probably the most undesirable side-effect although Telimaa *et al.* (1987) noted no such increase with 100 mg of MPA daily. If weight increase is due to fluid retention (Ganzina & Robustelli Della Cuna 1982) it should disappear after the end of treatment. Alternatively, it may be related to increased appetite observed in women taking MPA (unpublished communication from Upjohn Ltd). Bloating was also more common in the MPA-treated groups but only caused temporary inconvenience. Overall, it seems that MPA is a well-tolerated progestogen which can safely be used at a higher dosage than is currently recommended for treatment of menstrual disorders.

The clinical implications of this study with regard to the management of women with pain due to pelvic congestion need to be summarized. Once the diagnosis has been securely established after laparoscopy, ultrasonography and pelvic venography have been performed, treatment with MPA may provide a means of temporary relief from a pain that has often been crippling for many years. In practice many women continue treatment for much longer than 4 months until they feel ready to tolerate a return of some pain. Previous studies have revealed the value of counselling women with pelvic pain by someone who is sympathetic to their problems and can give them sufficient time (Pearce *et al.* 1982). Long-term benefits of therapy have also been demonstrated in this study It would seem that a conservative approach is worthwhile for many young women in the management of this perplexing and disabling condition.

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Pregnancy screening by Doppler uteroplacental and umbilical artery waveforms

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Summary. Doppler waveforms from the uteroplacental and umbilical arteries were studied in 543 unselected women attending an antenatal clinic. Overall, 357 women were studied at 26–30 weeks and 395 at 34–36 weeks; 209 were studied at both gestation periods. Results were not made available to clinicians. There was no difference in outcome of pregnancies between those with normal and abnormal uteroplacental waveforms, but birthweights were significantly lower in those with an abnormal umbilical artery waveform at either gestation. There were no other statistically significant differences between groups. Although the power of the study to detect differences in outcome in this sample size is limited, our findings do not support the introduction of this new technique into clinical practice before sufficiently large randomized controlled trials have shown some benefit.

It is suggested that 36% of intrauterine deaths of normally formed singleton fetuses are associated with intrauterine growth retardation (IUGR) co-existing, or not, with pregnancy-induced hypertension (PIH) (Northern Regional Health Authority Coordinating Group 1984). Accurate prediction or early recognition of fetal compromise, by a screening technique applicable to all pregnancies, should facilitate management. Fetal measurement by diagnostic ultrasound has been shown to be an accurate method for identifying the small-for-gestational-age (SGA) fetus but its use as a screening test has not been shown to improve outcome in randomized studies (Neilson *et al.* 1984). Screening techniques to identify women at increased risk for developing PIH have proven disappointing (Redman 1982).

Doppler ultrasound is a relatively new technique which merits investigation as a screening method for IUGR and PIH since both conditions are associated with placental vascular pathology (Khong *et al.* 1986), and Doppler flow velocity waveforms obtained from the uteroplacental and umbilical arteries provide information about the haemodynamics on both sides of the placenta. These waveforms have been shown to be abnormal in some complicated pregnancies (Trudinger *et al.* 1985; Fleischer *et al.* 1985), although the specific pathophysiology which underlies the development of abnormal patterns is incompletely understood. IUGR and PIH may be associated with failure of the normal physiological invasion by the trophoblast into the myometrium which converts maternal spiral arteries into low-resistance vessels. This failure leads to higher vascular resistance on the maternal side of the placenta, which may in turn lead to alterations in the development of the fetoplacental vessels and obliteration of tertiary stem villus arterioles (Giles *et al* 1985).

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Table 1. Umbilical artery AB ratios and outcome

	26–30 weeks		34–36 weeks	
	Normal	Abnormal	Normal	Abnormal
n	326 (94·8)	18 (5·2)	356 (95·2)	18 (4·8)
Maternal age (years)				
Mean (SD)	26·8 (5·3)	27·9 (4·5)	27·0 (5·3)	25·4 (5·0)
Admitted or attended				
Day Unit	157 (48·2)	10 (55·6)	138 (38·8)	3 (16·7)
PIH	85 (26·1)	6 (33·3)	99 (27·8)	6 (33·3)
SGA	17 (5·2)	2 (11·1)	15 (4·2)	1 (5·6)
Gestation at delivery (weeks)				
Mean (SD)	39·1 (1·8)	38·3 (1·9)	39·5 (1·4)	38·9 (1·8)
Delivery before 37 weeks	23 (7·0)	3 (16·7)	9 (2·5)	1 (5·6)
Elective delivery	71 (21·7)	7 (38·9)	96 (30·0)	8 (44·4)
C/S before labour	14 (4·3)	3 (16·7)	21 (5·9)	3 (16·7)
C/S during labour	34 (10·4)	1 (5·6)	36 (10·1)	1 (5·6)
Total instrumental deliveries	128 (39·3)	7 (38·9)	126 (35·4)	7 (38·9)
Birthweight (kg) Mean (SD)	3·36 (0·52)	3·11 (0·60)*	3·39 (0·46)	3·03 (0·60)†
Apgar score				
<6 at 1 min	36 (11·0)	2 (11·1)	31 (8·7)	3 (16·7)
<6 at 5 min	3 (0·9)	0	4 (1·1)	0
Admitted NICU	18 (5·5)	4 (22·2)	11 (3·1)	2 (11·1)

*P<0·05.

†P<0·002.

Results are *n* (%) or mean (SD) values as appropriate.

PIH, Pregnancy-induced hypertension; SGA, small-for-gestational-age; C/S, caesarean section; NICU, neonatal intensive care unit.

However, most clinical studies of the use of Doppler ultrasound have investigated pregnancies already identified as at increased risk, so that the prevalence of abnormal waveforms in an unselected population is unknown. Furthermore, there is no published information about the value of measuring uteroplacental and umbilical artery waveforms simultaneously in unselected pregnancies.

We present the results of the first phase of a study to ascertain whether Doppler velocimetry does have potential as a screening test for IUGR and PIH.

Subjects and methods

All women attending the antenatal clinic at either of two gestational age periods, 26–30 weeks and 34–36 weeks, were invited to participate in the study by one of us who performed all of the examinations (M.P.).

Uteroplacental and umbilical artery waveforms were obtained, in the antenatal clinic, using a hand-held 4-MHz continuous-wave directional Doppler system, with real-time spectral analysis (Angioscan III). Conventional real-time ultrasound was not used.

All measurements were performed with the patient in the semi-reclining position to avoid the risk of supine hypotension. To eliminate the possibility of inadvertently including maternal signals from the epigastric or iliac vessels the ultrasound transducer was moved until uteroplacental waveforms representing lowest resistance were obtained (Hanretty *et al.* 1988). Umbilical artery waveforms were obtained during periods of fetal apnoea, and the systolic/diastolic ratio (AB ratio) (Stuart *et al.* 1980) was calculated when five representative consecutive waveforms had been obtained from each vessel. In all instances measurements were made when waveforms of greatest clarity showing the highest frequency envelope were obtained and, in the umbilical artery, when venous contraflow was seen in the other channel.

Overall, 357 women were studied at the earlier, and 395 at the later gestation; of these, 209 patients were studied at both. No satisfactory umbilical artery or uteroplacental waveforms could be obtained from 13 (4%) and 66

(18%) women respectively at 26–30 weeks, and from 21 (5%) and 77 (19%) at 34–36 weeks.

The AB ratio was defined as abnormal if it was greater than the 95th centile, calculated previously from a pilot study of 150 patients. The Doppler results were not available to clinicians. End points studied are shown in Tables 1 and 2.

Patients were classified clinically as having PIH if, following a blood pressure recording of ≥140/90 mmHg, the obstetrician arranged for further investigation or treatment. Babies with birthweights <5th centile, determined from a large local database (Forbes & Smalls 1982), were categorized as SGA.

Comparisons were made between those with normal and abnormal waveforms using Student's *t*-test for continuous variables and the χ^2 or Fisher's exact probability test for categorical data. *P*<0·05 was considered significant.

Results

Tables 1 and 2 show pregnancy outcome after Doppler study of umbilical and uteroplacental artery waveforms at both gestation periods. From the pilot study, values for the umbilical artery AB ratio above 4·11 and 3·86 were considered abnormal at the first and second screening periods respectively. For the uteroplacental artery the cut-off values were 2·07 and 2·00 respectively. The mean birthweight was significantly less in the groups with abnormal umbilical artery AB ratios. There were no other significant differences.

In 10 pregnancies there was no identifiable forward flow at the end of diastole on at least one occasion. The details of these pregnancies are summarized in Table 3. Although previous reports of this finding have shown a close association with fetal and neonatal death (Hsieh *et al.* 1988) all babies but one were born in good condition. The exception had an Apgar score of only 1 at 1 min following cord prolapse and breech extraction; the Apgar score was 7 at 5 min and the baby did well subsequently.

The only perinatal death in the study occurred in a baby with gastroschisis who was born at 38 weeks and died the day after surgery. Both uteroplacental and umbilical artery waveforms had been normal when this baby was studied at 36 weeks.

Discussion

This is the first reported study which examines the use of both uteroplacental and umbilical

Table 2. Uteroplacental artery AB ratios and outcome

	26–30 weeks		34–36 weeks	
	Normal	Abnormal	Normal	Abnormal
n	272 (93·5)	19 (6·5)	309 (97·2)	9 (2·8)
Maternal age (years)				
Mean (SD)	26·6 (5·3)	29·1 (5·6)	27·0 (5·0)	24·5 (5·1)
Admitted or attended				
Day Unit	128 (47·1)	9 (47·4)	138 (44·7)	3 (33·3)
PIH	65 (23·9)	5 (26·3)	80 (25·9)	4 (44·4)
SGA	15 (5·5)	1 (5·3)	16 (5·2)	0
Gestation at delivery (weeks)				
Mean (SD)	39·1 (1·7)	38·2 (2·2)	39·5 (1·4)	39·3 (1·1)
Delivery before 37 weeks	18 (16·6)	4 (21·1)	6 (1·9)	0
Elective delivery	54 (19·9)	6 (31·6)	83 (26·9)	3 (33·3)
C/S before labour	9 (3·3)	2 (10·5)	20 (6·5)	0
C/S during labour	31 (11·4)	1 (5·3)	30 (9·7)	0
Total instrumental deliveries	102 (37·5)	8 (42·1)	106 (34·3)	2 (22·2)
Birthweight (kg) Mean (SD)	3·36 (0·52)	3·27 (0·45)	3·38 (0·48)	3·38 (0·33)
Apgar score				
<6 at 1 min	30 (11·0)	3 (15·8)	29 (9·4)	1 (11·1)
<6 at 5 min	2 (0·2)	0	4 (1·3)	0
Admitted NICU	18 (6·6)	2 (10·5)	10 (3·2)	0

Results are *n* (%) or mean (SD) values as appropriate.

PIH, Pregnancy-induced hypertension; SGA, small-for-gestational-age; C/S, caesarean section; NICU, neonatal intensive care unit.

artery waveforms as a screening test in an unselected population. The gestational age periods selected for screening were chosen in order to determine whether Doppler might identify pregnancies at high risk at a stage when intensive monitoring, or intervention as indicated by standard techniques, would be indicated in the fetal interest. The possible value of screening even earlier in pregnancy has been assessed by Campbell *et al.* (1986) who used Doppler uteroplacental waveforms as a screening test early in the second trimester and showed a higher rate of complications in those with abnormal waveforms. However, they found abnormal waveforms in 40% which suggests that their normal ranges were not applicable to the study population. In our study, between 3 and 6% had AB ratios >95th centile, calculated for both vessels at both gestation periods, indicating that the ranges obtained from the pilot study were appropriate.

The use of a continuous wave system to study uteroplacental vessels has recently been questioned by Campbell *et al.* (1988), but our findings should be contrasted with previous smaller studies, using similar equipment, which showed an association between IUGR and PIH in patients with abnormal waveforms (Trudinger *et al.* 1985; Fleischer *et al.* 1985). The high overall frequency of PIH reflects the use of the diagnostic criteria used by clinicians in managing these patients (Redman & Jefferies 1988).

There were no differences in outcome between those with abnormal and normal uteroplacental waveforms. Uteroplacental vascular pathology is focal (Khong *et al.* 1986) and it seems unlikely that the use of waveforms from any individual vessel will be informative about the overall degree of vascular damage.

Study of an unselected obstetric population has failed to demonstrate a higher frequency of adverse outcome among babies with abnormal umbilical artery AB ratios.

However, although there was no difference in the proportion of babies categorized as SGA between those with normal and abnormal umbilical artery waveforms, the latter finding was associated with lower mean birthweight. It is possible that the umbilical artery waveform identifies babies who have not fulfilled their genetic growth potential and have experienced intrauterine growth retardation whilst not necessarily being SGA. Similarly, babies which are below an arbitrary birthweight centile value, whilst by definition being SGA, may not have been growth retarded *in utero,* and the possibility that Doppler may distinguish the truly growth-retarded fetus from those which are designated as SGA requires further study.

Forward blood flow in the umbilical artery is normally found throughout the cardiac cycle from early in the second trimester, and absence of end diastolic flow has been associated with severe fetal compromise and high perinatal mortality in pregnancies identified as being at high risk (Hsieh *et al.* 1988; Woo *et al.* 1987). Although this pattern was seen in two pregnancies which resulted in the birth of SGA babies (Table 3), there were no losses. Our results suggest that the finding of absent end diastolic velocities should not be considered as an indication for immediate delivery (Woo *et al.* 1987).

Our findings are consistent with the only published randomized controlled trial of umbilical

Table 3. Outcome in pregnancies with absent end diastolic velocities in the umbilical artery

AB ratio		Birthweight (g)	SGA	Apgar score	
26–30 weeks	34–36 weeks			At 1 min	At 5 min
AEDV	ND	2·89	No	9	9
AEDV	ND	3·80	No	9	9
AEDV	ND	1·60	Yes	9	9
AEDV	2·23	3·21	No	9	9
AEDV	AEDV	3·82	No	9	10
AEDV	AEDV	3·42	No	9	10
1·92	AEDV	2·31	No	8	9
4·27	AEDV	2·48	No	1	7
ND	AEDV	3·50	No	9	10
ND	AEDV	1·40	Yes	7	9

AEDV, Absent end diastolic velocity; ND, not done; SGA, small-for-gestational-age.

artery velocimetry. The only differences in outcome attributable to the availability of Doppler results to clinicians in that study of 300 pregnancies were a lower frequency of fetal distress and caesarean section during labour (Trudinger *et al.* 1987).

Our results demand that Doppler ultrasound be rigorously assessed before it is used to guide clinical management. The second phase of our study is a randomized controlled trial to assess the effect of the availability of Doppler results on fetal outcome and obstetric management.

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Correlation between Doppler flow velocity waveforms and cord blood viscosity

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Summary. The contribution of rheological factors to the impedance of blood flow in the umbilical artery as determined by continuous-wave Doppler ultrasound was investigated. Of the 51 pregnancies recruited, six were complicated by pre-eclampsia, 10 by intrauterine growth retardation, 15 by both pre-eclampsia and fetal growth retardation, and there were 20 controls. A significant correlation was demonstrated between both plasma viscosity and gestational age and the resistance index used to characterize the Doppler waveform. Multiple regression analysis demonstrated that changes in plasma viscosity explained 55% of the variance seen in the resistance index and that this was statistically significant. This finding is, however, unlikely to be of clinical significance as whole blood viscosity had an insignificant effect on the impedance in the umbilical artery. We postulate that vascular factors such as the number and calibre of the placental arterioles are a more important determinant of umbilical artery impedance.

Doppler ultrasound is currently under review for assessing fetal circulation in high-risk pregnancies. Doppler-shifted signals from an umbilical artery are displayed as a flow velocity waveform which can then be analysed to produce a measure of downstream, or placental, resistance to blood flow. High values of resistance have been shown to have an association with fetal intrauterine growth retardation (for review, see McParland & Pearce 1988). The components of downstream resistance (impedance) to umbilical artery blood flow will include a vascular factor and a rheological or viscosity factor. This study set out to determine the extent of the rheological contribution to umbilical artery impedance in both normal and complicated pregnancies.

Patients and methods

The study included 51 pregnant women who underwent Doppler ultrasound studies of the umbilical artery. They comprised six women with pre-eclampsia, defined as a sustained arterial blood pressure of ≥140/90 mmHg occurring for the first time in the second half of pregnancy, with or without proteinuria; 10 with intrauterine growth retardation (IUGR), defined as ultrasound evidence of fetal abdominal circumference > 2 SD below the mean for gestational age according to Campbell (1974); 15

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women with both pre-eclampsia and IUGR; and 20 women without a condition associated with uteroplacental insufficiency (controls). None smoked cigarettes or was diabetic, and all women were in-patients at the time of the Doppler studies. All but one woman had ultrasonic confirmation of gestational age before 20 weeks gestation. Doppler ultrasound studies of flow resistance in the umbilical artery were at a median of 1 day before delivery (range 0–5 days) with the woman resting in a semirecumbent position. A continuous-wave Doppler ultrasound machine with 4-MHz transducer (Doptek Ltd, Chichester, UK) was used to obtain the characteristic flow velocity waveforms of the umbilical artery. Measurements were made of the systolic/diastolic ratio (A/B ratio) and the resistance index (RI) of the maximum velocity envelope, taking a mean of five cardiac cycles chosen because of a high signal-to-noise ratio. All signals were obtained during fetal apnoea diagnosed by a steady state flow in the umbilical vein recording from the reverse channel of the spectrum analyser.

At birth the infant was held at the same level as the placenta and the cord clamped and divided within 15 s of delivery. Before delivery of the placenta, 10 ml blood were taken from a cord vessel using a syringe and 16G needle and divided between two 10 ml bottles anticoagulated with K-EDTA, resulting in a final concentration of 3 mg/ml. The bottles were then agitated thoroughly and kept at room temperature. Rheological studies were done within 4 h.

Blood viscosity measurement

Whole blood viscosity was measured at shear rates of 0·945 s^{-1} (low shear, LS) and 94·5 s^{-1} (high shear, HS) using a Contraves LS30 rotational viscometer (Contraves Industrial Products Ltd, Ruislip, Middlesex), and plasma viscosity was measured using a Coulter-Harkness capillary viscometer (Coulter Electronics Ltd, Harpenden, Essex); both viscometers were operated at 37°C.

After centrifugation of the blood at 1500 *g* for 10 min, red cells were harvested from the centre of the packed cell column and suspended in phosphate-buffered saline (Dulbecco A, Oxoid Ltd, London) at approximately 25% haematocrit. The haematocrit of this suspension and of the whole blood was measured using a Coulter Counter (model S plus IV), and the red cell suspension was adjusted to 10%. Red cell filterability was assessed using a St George's Filtrometer (Carri-Med Ltd, Dorking, Surrey) and 5-μm nuclepore filters from a single batch. The instrument measures the rate of flow of the red cell suspension through the filter at fixed intervals soon after the start of flow. It automatically computes the initial rate of flow (Dormandy 1985). From this measurement and the known haematocrit, the red cell transit time (RCTT) is calculated; this characterizes the rate of flow of pores occupied by red cells compared to those where suspending medium only is present. For the levels of residual white cells in the red cell suspension obtained in this study (<100/μl), the RCTT value is independent of pore blockage by contaminating particles (Dormandy 1985).

Statistical analysis

One-way analysis of variance was used to compare the mean values for each diagnostic group, and Duncan's multiple range test was then used to compare all pairs of means. Correlation analysis was used to investigate the possible interrelations between gestational age, Doppler flow resistance and cord blood rheology. Multiple regression analysis was used to investigate the relation between these three variables.

Results

All women were delivered within 5 days of the Doppler studies and most of them by caesarean section. Those undergoing elective caesarean section for indications not associated with uteroplacental insufficiency (e.g. previous caesarean section, breech presentation) provided useful controls since Doppler studies could be performed the day before delivery, and cord blood could be analysed at a convenient time of day. All these women had infants with birthweight appropriate for gestation. The indications for caesarean section in the complicated groups were because of the diagnosis and were generally emergency procedures. One patient in the IUGR group, one in the pre-eclampsia with IUGR group, and one in the pre-eclampsia-only group had vaginal deliveries.

In one woman in the IUGR group, two in the pre-eclampsia group, and in five in the pre-eclampsia with IUGR group, the A/B ratio or RI could not be calculated since there were absent end-diastolic frequencies. In addition, one case

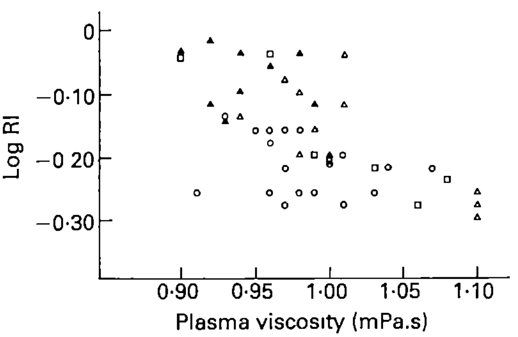

Fig. 1. Correlation between log resistance index (RI) and plasma viscosity in pregnancies complicated by intrauterine growth retardation (Δ), pre-eclampsia (□), both pre-eclampsia and intrauterine growth retardation (▲) and control pregnancies (O).

in the pre-eclampsia with IUGR group demonstrated reversal of flow during diastole. As it is known that such Doppler findings represent a worsening of the fetal condition (McParland & Pearce 1988) we assigned RI values of 0·90 to absent end-diastolic frequencies, and 0·95 to reversal of flow, because these values were higher than any observed, and appeared to fit the distribution (Fig.1).

The distributions of A/B ratio and of RI values were highly skewed, but the distribution of the logarithmically transformed (to the base 10) RI values approximated to normal. This transformation was therefore performed before the relations between the RI and diagnostic groups was examined.

Table 1 shows the mean (SD) values for gestational age, Doppler blood flow resistance and rheological determinants. The patient of uncertain gestational age is excluded from analysis where gestational age was taken into account. All rheological determinations were not always possible on every sample because of insufficient blood, or small clots in the plasma.

There were significant differences in log RI ($P<0{\cdot}01$), gestational age ($P<0{\cdot}01$), and plasma viscosity ($P<0{\cdot}05$) between the pre-eclampsia with IUGR group and all other groups. The pre-eclampsia with IUGR group had a lower mean gestation at delivery because of the need for intervention on clinical grounds.

If all three complicated groups are pooled, a higher haematocrit and whole blood viscosity at low shear are shown, compared with the control group, but these differences are not statistically significant. Correlations of gestational age and rheological determinants with log RI are shown in Table 2, demonstrating a significant correlation of gestational age and plasma viscosity with log RI. There was no significant correlation between other rheological parameters and log RI, when all patients were considered together, but in the control group gestational age correlated significantly ($P<0{\cdot}05$) with plasma vis-

Table 1. Gestational age, Doppler blood flow, resistance and rheological determinants according to diagnostic group

Patient group	Gestational age (weeks)	RI	Log RI	WBV (mPa.s) HS	WBV (mPa.s) LS	Haematocrit (%)	Plasma viscosity/ (mPa.s)	RCTT
Control								
n	20	20	20	19	19	20	19	17
Mean	36·40	0·61	−0·22	4·61	17·35	45·03	0·98	11·05
(SD)	(3·53)	(0·68)	(0·05)	(0·81)	(6·22)	(5·73)	(0·04)	(0·88)
IUGR								
n	10	10	10	10	10	10	10	6
Mean	35·90	0·69	−0·17	4·89	22·45	46·79	1·01	10·73
(SD)	(3·03)	(0·14)	(0·09)	(0·64)	(6·72)	(2·91)	(0·06)	(1·29)
PE								
n	5†	6	6	6	6	6	6	5
Mean	34·56	0·69	−0·17	4·58	18·18	46·82	1·00	10·51
(SD)	(4·60)	(0·17)	(0·10)	(0·59)	(5·50)	(2·03)	(0·07)	(0·85)
PE with IUGR								
n	15	15	15	15	15	15	10	11
Mean	31·00**	0·81	−0·099**	4·85	19·78	48·75	0·95*	11·09
(SD)	(2·47)	(0·12)	(0·07)	(0·72)	(6·65)	(5·82)	(0·03)	(1·22)

† One patient of uncertain gestational age excluded, *$P<0{\cdot}05$, **$P<0{\cdot}01$. RI, Resistance index; WBV, whole blood viscosity; HS, high shear, LS, low shear; RCTT, red cell transit time; IUGR, intrauterine growth retardation; PE, pre-eclampsia.

Table 2. Correlations of gestational age and rheological parameters with log RI (all patients)

	r	*P*
Gestational age	−0·61	<0·0001
WBV (HS)	−0·04	0·75
WBV (LS)	−0·06	0·67
Haematocrit	0·08	0·57
Plasma viscosity	−0·60	<0·0001
RCTT	0·19	0·23

For abbreviations see Table 1.

cosity (r=0·54), whole blood viscosity at high shear rate (r=0·49) and whole blood viscosity at low shear rate (r=0·52).

Considering all patients, plasma viscosity and gestational age were also correlated (r=0·68, P<0·0001). Since only gestational age and plasma viscosity are related to log RI (Table 2), we investigated the relation between these variables and the effect of diagnostic groups by multiple regression.

Table 3 shows that plasma viscosity had a significant effect on log RI after allowing for gestational age. After allowing for both gestational age and plasma viscosity there was a significant relation between log RI and diagnostic group. This shows that the RI was higher in all complicated groups than in controls. There was very little difference between the RI in IUGR and pre-eclampsia groups, although the greatest mean RI was for those patients with both pre-eclampsia and IUGR.

Discussion

Doppler ultrasound provides a means of investigating the fetal circulation, and analysis of the Doppler-shifted flow velocity waveform provides a measure of downstream resistance (or impedance) to flow (Skidmore & Woodcock 1980). An association between increased impedance in the fetal circulation and IUGR has been described by several authors.

Associations have also been reported to exist between abnormal fetal blood rheology and pre-eclampsia with or without IUGR. Buchan (1981, 1982) reported a higher mean whole blood viscosity, haematocrit and fibrinogen concentration in outcomes of pregnancies complicated by pre-eclampsia and IUGR than in controls. These infants also had a lower mean birthweight. Black & Lubchenco (1980) reported 112 infants with the neonatal hyperviscosity syndrome and found a high proportion was associated with maternal pre-eclampsia.

Impedance to blood flow resistance depends upon both a vascular factor and a rheological factor. The purpose of this study was to establish the contribution of the rheological factor to impedance as measured by Doppler ultrasound in both normal and complicated pregnancies. We chose to subdivide our patients into diagnostic groups to differentiate between severe and mild pre-eclampsia. Women who suffer both pre-eclampsia and IUGR can all be considered to be suffering from severe pre-eclampsia (Gant & Pritchard 1986) and this was certainly borne out in the severity of their clinical signs. Those with pre-eclampsia alone tended to have milder signs and appropriately grown infants, and may well be part of a separate clinical entity.

Giles & Trudinger (1986) studied cord blood viscosity in relation to the A/B ratio obtained by Doppler ultrasound but neglected to perform a statistical correlation analysis, and made no allowance for the effect of gestational age. It is well established that indices of resistance from umbilical artery waveforms decrease with advancing gestation (Stuart *et al.* 1980; Trudinger *et al.* 1985; Pearce *et al.* 1988). Variation

Table 3. Analysis of variance for multiple regression (with log RI as dependent variable)

Source	Degrees of freedom	Sum of squares	Mean square	*F* ratio	*P*
Total regression	43	0·28383			
	5	0·17194	0·03439	11·68	<0·001
Gestational age	1	0·10355	0·10355	35·17	<0·001
Plasma viscosity (given gestational age)	1	0·01527	0·01527	5·19	<0·05
Diagnostic group (given gestational age and plasma viscosity)	3	0·05312	0·01771	6·01	<0·01
Residual	38	0·11189	0·00294		

in cord blood rheology with advancing gestational age has also been described (Buchan 1984; Bratteby 1968), viscosity measurements tending to increase with gestation. This is confirmed in our study by correlation analysis (Table 2), and gestational age must be controlled for in considering the effect of rheological factors on impedance.

Our results demonstrate a significant negative correlation of plasma viscosity with the RI, persisting after adjustment for gestational age, but no other rheological parameters appeared to bear a consistent relation with the RI, suggesting that the vascular factor may be more significant in determining impedance in the placental circulation. Giles *et al.* (1985) describe an association between a high A/B ratio and obliteration of fetal arterioles in the tertiary stem villi of the placenta. This pathological finding in the vessels downstream from the umbilical arteries is likely to have a far greater influence upon the flow resistance than small alterations in blood viscosity. Recently, Trudinger *et al.* (1987) showed that embolization of the umbilical circulation in lambs by means of microspheres produces an increase in A/B ratio, demonstrating that changes in peripheral resistance have marked effects on flow velocity waveforms.

Although a correlation between RI and plasma viscosity was demonstrated, the actual differences in plasma viscosity are small and it is unlikely that the association of plasma viscosity with flow resistance measurement is of any clinical significance. This is supported by the absence of any correlation between whole blood viscosity and RI. The lack of effect of changes in viscosity on flow velocity waveforms is also observed in the maternal circulation (Steel *et al.* 1988).

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Outcome of pregnancies complicated by severe hypertension and delivered before 34 weeks; stepwise logistic regression analysis of prognostic factors

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Summary. The outcome is described for 106 patients with severe hypertension in pregnancy requiring delivery between 26 and 34 weeks. Management was with methyldopa, hydralazine when required and delivery by caesarean section when indicated. Most patients were delivered for cardiotocographic fetal distress or unstable maternal blood pressure. Eighty-five babies (80%) survived and were well at follow-up at 1 year; the perinatal mortality was 123/1000 total births. One patient had postpartum eclampsia, one had pulmonary oedema and one had transient renal failure, but all mothers left hospital well. Stepwise logistic regression analysis showed that the primary positive factor for survival of a healthy baby was gestational age, which was strongly correlated with birthweight. The need for caesarean section as an emergency, hypotension after parenteral hydralazine, intrauterine growth retardation, and severe proteinuria were adverse factors. Intraventricular haemorrhage had a major adverse effect on neonatal survival; it was predisposed to by prolonged maternal hypertension and by low gestational age.

This report concerns the outcome of 106 singleton pregnancies complicated by severe hypertension, including 100 with significant proteinuria, managed with a consistent treatment protocol. Multiple perinatal variables have been analysed for their association with outcome, using a stepwise logistic regression programme, to provide information on management decisions. This approach permits elimination of interacting and confounding factors and isolation of relevant primary variables.

Hammersmith Hospital has a Regional Neonatal Intensive Care Unit and receives 'in-utero transfer' of patients from other hospitals. Assessment of neonatal outcome is by a consistent clinical and pathophysiological approach (Wigglesworth 1980), with complete neonatal and infant neurological assessment (De Vries *et al.* 1985).

Patients and methods

A total of 106 patients with singleton pregnancies complicated by severe hypertension and

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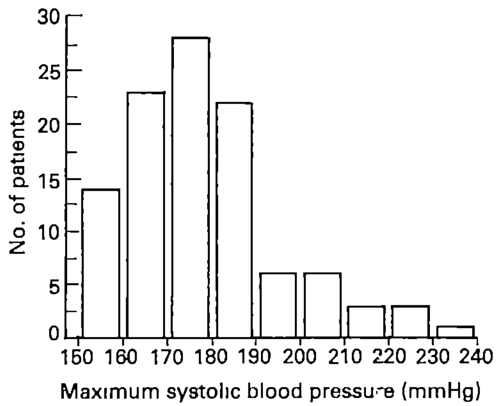

Fig. 1. Maximum systolic blood pressures recorded in 106 patients with severe hypertension in pregnancy.

delivered before 34 weeks was managed at Hammersmith Hospital between 1 January 1982 and 31 December 1985. Of these, 86 had been transferred '*in utero*'; the other 20 had originally been booked at the hospital.

Criteria for entry

The diagnosis of severe hypertension approximated to that proposed by Davey *et al.* (1984) and was based on the following criteria. Diastolic blood pressure ⩾ 120 mmHg or ⩾ 110 mmHg on two consecutive occasions 6 h apart, or ⩾ 95 mmHg plus one or more of the following: (a) proteinuria ⩾ 3 g/24 h; (b) oliguria < 500 ml/24 h; (c) symptoms and signs of imminent eclampsia; (d) eclamptic fit; (e) rapid development of generalized oedema. All patients had systolic blood pressures ⩾ 150 mmHg and all needed to be delivered before 34 weeks. In addition, to satisfy the definition of pregnancy-induced hypertension from the American College of Obstetricians and Gynecologists (Hughes 1974) all patients had to have had a rise of ⩾ 30 mmHg in systolic pressure and ⩾ 15 mmHg in diastolic pressure from values obtained before 20 weeks pregnant. The distribution of maximum systolic blood pressures recorded is shown in Fig. 1.

Significant proteinuria was diagnosed on a 2+ result on urine testing with a multiple reagent strip (Multistix, Ames) and severe proteinuria was defined as a 3+ or 4+ result or a total urinary protein excretion >3 g/24 h urine collection.

The mean age of the patients was 27·5 years (SD 5·7, range 16–39); 55 (52%) were primigravid and 51 (48%) multigravid. Fifty-eight were European white, 23 Negro, 24 Asian and 1 Oriental.

Gestational age was from the first day of the last menstrual period; early ultrasound scans were usually available for confirmation. If there was a clear discrepancy, the early ultrasound result was favoured.

Classification

This was based on the definitions of Davey & MacGillivray (1987). Forty-nine (89%) of the primigravidae and 36 (71%) of the multigravidae had gestational proteinuric hypertension (pre-eclampsia) (Table 1). To detect previously unsuspected chronic renal disease, patients with hypertension of onset before 20 weeks pregnant had creatinine clearances and renal ultrasound scans performed; urinary vanillyl-mandelic acid estimations were used to exclude phaeochromocytoma.

Fetal monitoring

Antenatal ultrasound scans used a Hitachi portable machine with both 3·5 and 5 MHz real-time linear array. Patients were scanned on admission and at 7–10-day intervals thereafter. Biparietal diameter was measured in all and placental site assessed. From mid-1983 onwards abdominal circumference was also measured and amniotic fluid volume assessed. For consistency in this analysis, biparietal diameters alone were used to define intrauterine growth retardation (<10th centile), and related to centile charts determined for the hospital population.

Cardictocograms were recorded at least twice

Table 1. Classification of hypertension

	Number
Gestational proteinuric hypertension	85
Gestational hypertension	6
Chronic hypertension	6
Chronic renal disease (with hypertension)	3*
Chronic hypertension with superimposed pre-eclampsia	6†
Total	106

*Two had systemic lupus erythematosus; one had chronic glomerulonephritis.

†One had systemic lupus erythematosus.

daily in the antenatal ward and more frequently or continuously where hypertension merited monitoring more intensively on the labour ward. They were appraised visually as normal, suboptimal, unprovoked decelerations or terminal (Visser & Huisjes 1977) and all the traces were reviewed retrospectively by one of the authors (R.J.D.).

Maternal monitoring

Blood pressures were recorded 4-hourly if regarded as controlled, hourly or more frequently if not. Urines were tested daily and intake–output charts were maintained. If there was significant proteinuria every specimen was tested. Full blood counts and biochemical profiles were obtained twice a week, and daily if close monitoring on the labour ward was indicated. Liver function tests including serum albumin were performed at least once on all patients and repeated if indicated. Coagulation screens were done when indicated by bleeding, suggestion of concealed placental haemorrhage, thrombocytopenia or intrauterine fetal death.

Six patients developed thrombocytopenia (platelets $<100\times10^9$/l) without any clinical manifestations; another with thrombocytopenia had an episode of epistaxis and of haematuria; yet another had elevated plasma bilirubin and hepatic enzymes. Two more had the HELLP syndrome as defined by Weinstein (1982), with thrombocytopenia, evidence of intravascular haemolysis and deranged liver function; one of these had an episode of haematuria. One other patient was admitted at 33 weeks with disseminated intravascular coagulation; and another with anticardiolipin antibodies developed bone marrow necrosis and pancytopenia.

Therapeutic management

Methyldopa, in divided doses totalling between 500 mg and 3 g/24 h, was the drug of choice for the long-term control of blood pressure and was given to 62 patients. The average dose before delivery was 1·5 g/day. In general, patients who had been given other hypotensive drugs at other hospitals were changed to methyldopa within 24 h of admission if they were undelivered. For initial control of patients transferred with high blood pressure, parenteral hydralazine was the drug of choice, 5–10 mg being given every 30 min until blood pressure was stabilized at about 140/90 mmHg. A hypotensive episode after hydralazine was defined by a fall in the mean arterial pressure of 35 mmHg from the mean of the previous four readings, within 30 min of hydralazine administration. Towards the end of 1985, intermittent titrated small volume intravenous infusions of hydralazine given by very slow injection or infusion pump were introduced. If methyldopa alone did not effect adequate control, atenolol, 50–100 mg 12-hourly (19 patients), or oxprenolol (7 patients) was added to the regimen. Patients with symptoms or signs of imminent eclampsia, an unstable blood pressure, or anxiety or restlessness were given phenobarbitone (45 patients) or diazepam (18 patients). Four patients had been given diuretics before being admitted from other hospitals; these were discontinued on admission. Five proteinuric patients with plasma albumin <25 g/l were given daily intravenous infusions of salt-free human serum albumin (Albuminar-20, Armour) for a few days before delivery to maintain intravascular volume.

All patients were intended to receive 12 mg dexamethasone intramuscularly, two doses 24 h apart, at about 28 weeks gestation, repeated weekly until 32 weeks (Lamont *et al.* 1983). Seventy-six completed at least one full course of dexamethasone before delivery; eight others had incomplete courses.

Delivery

Patients were reviewed daily by senior staff (consultant or senior registrar) to assess the need for delivery; 102 patients were delivered by caesarean section under general anaesthesia. Three began premature labour spontaneously without evidence of fetal compromise and labour was allowed to proceed; labour was induced in one patient with an intrauterine death.

Primary indications for delivery by caesarean section were cardiotocographic fetal distress (46 patients), suboptimal cardiotocograms (8), intrauterine growth retardation (4), unstable maternal blood pressure (30), antepartum haemorrhage (4), coagulopathy (4), deteriorating HELLP syndrome (1), increasing proteinuria (2), onset of preterm labour with breech presentation (2), and history of intrauterine death at 34 weeks in a previous pregnancy (1).

Deliveries were classified on clinical grounds—if it was felt that delivery must be effected in ≤ 4 h this was an emergency; if delivery was indicated in 4–24 h this was termed 'elective'.

Neonatal assessment

The babies were resuscitated by a paediatrician present at birth. Birthweight and Apgar scores were recorded but the latter are not included in the outcome analysis as most babies were intubated electively. All liveborn babies were transferred to the neonatal intensive care unit.

Cranial ultrasound scans were performed daily for a week, using a mechanical sector scanner (A.L.T. mark III) with a multifrequency scan head. The cranial ultrasound findings were divided according to Levene *et al.* (1985) into nine grades: (1) normal; (2) germinal layer haemorrhage only; (3) intraventricular haemorrhage grades I and IIa; (4) isolated ventricular dilatation; (5) intraventricular haemorrhage grade IIb; (6) intraventricular haemorrhage grade III; (7) periventricular flares persistent after 48 h; (8) periventricular leukomalacia; (9) infarction. The first four grades were considered benign; grades 5–9 were considered serious.

Surviving infants were followed up at Hammersmith Hospital at the time of their expected birth and at 6, 9 and 12 months of age. The babies had a Griffiths (1970) mental development scale applied and neurological assessments based on items from Touwen (1979) and Amiel-Tison & Grenier (1980).

Maternal management postpartum

The anaesthetist was requested to ensure that the patient's systolic blood pressure was 100–150 mmHg and that she had received an anticonvulsant, sodium phenobarbitone or diazepam, before she recovered consciousness. Postoperatively systolic blood pressure was controlled below 150 mmHg with 4-hourly intramuscular hydralazine when required initially and oral methyldopa subsequently. Anticonvulsant treatment, generally with phenobarbitone, was continued for 24 h. Intravenous fluids were restricted to 1 litre plus output in the first 24 h; nearly all patients were taking fluids orally by then and intravenous fluids were discontinued. Neither indwelling catheters nor diuretics were used. After 24 h, the few patients in whom diuresis was not starting and urinary output had been <500 ml since the operation had renal investigations, and the use of frusemide and intravenous fluids was considered.

Statistical analysis

This was undertaken to identify prognostic factors and management variables related to outcome. Neonatal outcome was defined as normal or poor. The latter included intrauterine deaths, early and late neonatal deaths, infant deaths directly attributable to morbidity arising perinatally, and severe developmental and physical handicap.

In a preliminary study, a wide range of factors was examined in relation to outcome by χ^2 analyses for nominal data or by unpaired *t*-tests for continuous data (Hawkins & Derham 1988).

Factors not found to relate to neonatal outcome included: maternal age; parity; race; diagnostic classification; gestational age at first antenatal visit (before or after 18 weeks); blood pressure at first antenatal visit, systolic or diastolic; 'in-utero' transfer; duration of hospital admission; duration of hypertension; duration of significant proteinuria; administration of dexamethasone; maximum hypertension, systolic or diastolic; mean blood pressures in the 24 h before delivery, systolic or diastolic; use and dose of methyldopa, atenolol or parenteral hydralazine in the 24 h before delivery.

The primary indications for delivery, fetal distress, unstable blood pressure, biochemical or haematological deterioration, antepartum haemorrhage, intrauterine growth retardation, suboptimal cardiotocogram and others, did not differ in frequencies between normal survivors and 'poor outcome' babies.

Obstetric factors which appeared to be related to poor neonatal outcome were: intrauterine growth retardation (P = 0·06); severe proteinuria (P <0·05); use of diuretics (P = 0·001); use of phenobarbitone (P <0·05); use of diazepam (P <0·05); hypotensive episodes after intramuscular hydralazine (P <0·01); number of hypotensive drugs needed to control maternal hypertension (P <0·05); antepartum bleeding (P <0·05); cardiotocographic decelerations (P <0·01); emergency caesarean section *versus* elective (P <0·01). Duration of pregnancy at delivery (P <0·001) and birthweight (P <0·05) were directly related to a normal outcome. Since gestational age was more strongly associated with outcome than birthweight and the factor 'intrauterine growth retardation' covered the association between the two, birthweight was not considered further as a primary factor in the analysis.

The apparently positive antenatal variables were then entered into a stepwise regression (BMDPLR stepwise logistic regression program, BMDP Statistical Software, Inc., Los Angeles). A logistic regression is a development of multiple regression where the dependent variable is dichotomous rather than continuous, and therefore has a binomial distribution. The purpose of the stepwise procedure is to obtain a set of variables which are independently associated with outcome, although when variables are highly correlated, different sets of variables may be selected from different samples.

In the first stage of analysis it was clear that the factor most associated with outcome was duration of pregnancy at delivery ($P < 0{\cdot}001$). Other factors confirmed as being related to poor outcome in successive stages (Table 2) were emergency *versus* elective delivery, hypotensive episodes after intramuscular hydralazine, intrauterine growth retardation and severe proteinuria. After five stages the data were insufficient to derive further meaningful associations.

A preliminary χ^2 analysis indicated that intraventricular haemorrhage, determined in the newborn by ultrasound scans and graded as benign (grades 1–4) and serious (grades 5–9), was strongly related to neonatal outcome ($P < 0{\cdot}001$). A further stepwise logistic regression analysis was therefore conducted, excluding the two stillbirths and including the ultrasound findings, graded 1–9. In addition to the factors already isolated, the ultrasound gradings with respect to intraventricular haemorrhage were directly related to poor outcome ($P < 0{\cdot}01$). The relation of the occurrence of intraventricular haemorrhage (benign or serious) to the antecedent (antenatal) variables was examined by χ^2 analysis. There was, as expected, an inverse relation to duration of pregnancy at delivery ($P < 0{\cdot}05$); and the occurrence of benign and serious intraventricular haemorrhages was directly related ($P < 0{\cdot}05$) to the duration of hypertension during pregnancy.

Table 2. Stepwise logistic regression analysis of antepartum variables in relation to neonatal outcome, with duration of pregnancy at delivery as the primary variable

	Improvement in χ^{2*}	P value
Emergency caesarean section	11·69	0·003
Hypotensive episode after hydralazine	6·66	0·010
Intrauterine growth retardation	8·43	0·015
Severe proteinuria	8·74	0·033

*Indicates a value of the χ^2 statistic on one degree of freedom for improvement in the fit of the model when the corresponding variable is included in the predictor set.

Results

Maternal outcome

All 106 patients left hospital well. One woman developed severe pulmonary oedema postpartum and was treated successfully with frusemide. One developed renal failure postpartum; she recovered without the need for dialysis.

The mothers with haematological abnormalities were treated accordingly and most made satisfactory recoveries. The patient with disseminated intravascular coagulation had an eclamptic fit in preterm labour at 34 weeks; there were no physical maternal sequelae but the baby died. The patient with anticardiolipin antibodies and bone marrow necrosis was treated with steroids and made a slow recovery over 2 months but was left with autoimmune nerve deafness.

Perinatal outcome

Eighty-five babies (80%) survived and were normal and healthy on follow-up 1 year later. There were two stillbirths and 11 early neonatal deaths, giving an overall standard perinatal mortality rate of 123/1000 total births. There were three later neonatal deaths (1–4 weeks) and two infant deaths (>4 weeks), all in spastic babies; three babies were severely handicapped at 1 year of age, two being spastic and one hemiplegic. All these 21 babies were classified as having a 'poor outcome' for the purpose of analysis.

Only those variables isolated by the stepwise logistic regression, gestational age ($P < 0{\cdot}001$) and, by implication, birthweight, emergency caesarean section ($P < 0{\cdot}01$), hypotensive episodes after hydralazine, intrauterine growth retardation ($P < 0{\cdot}05$) and severe proteinuria

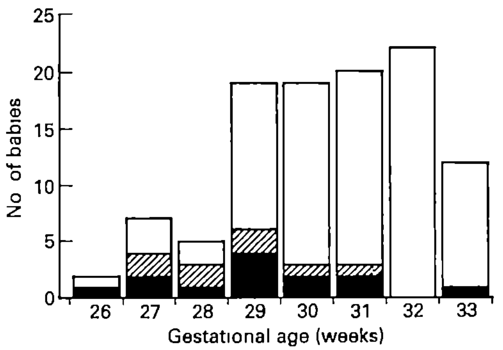

Fig. 2. Outcome in 106 singleton pregnancies complicated by severe hypertension. Gestational ages are to the nearest week. ■, Perinatal death; ▨, later death or spastic; □, normal.

(P <0·05), were considered as having primary importance as aetiological or prognostic factors. The apparent significance of the other variables giving a positive χ^2 value on the initial analysis may be attributed to their correlation with the factors mentioned.

Gestational age. The primary prognostic factor was duration of pregnancy at delivery (Fig. 2). Eight out of the 14 babies born at ≤ 28 weeks had a poor outcome and 20 of the 21 poor outcome babies were born before 32 weeks.

Birthweight. The relation between birthweight and outcome (Table 3) confirms the relation with gestational age, with the added component of intrauterine growth retardation, which was analysed separately.

Emergency caesarean section. Of the 76 babies born by emergency section 17 (22%) had a poor outcome; of the 26 born by elective section only 1 (4%) had a poor outcome. Most of the emergency caesarean sections were for fetal distress and antepartum bleeding, and the remainder for deteriorating maternal condition, so it is not surprising that the outcome was worse than in the elective group, where most sections were for failure of intrauterine growth without signs of immediate jeopardy to the baby. The data do not permit conclusions as to whether or not elective delivery earlier, with consequent reduction in maturity, might have been of advantage.

Hypotensive episodes after hydralazine. The use of parenteral hydralazine to control exacerbations of maternal hypertension was not of itself a bad prognostic factor, but if a hypotensive episode occurred (a drop of 35 mmHg in mean arterial pressure) this was associated with a poor neonatal outcome. Of 17 women with a poor outcome in whom hydralazine was used, 11 (65%) had had a hypotensive episode; of 70 with a good outcome who had had hydralazine, only 14 (20%) had had a hypotensive episode.

Intrauterine fetal growth retardation. This was associated with a poor neonatal outcome. Of the 21 babies with a poor outcome 90% were growth retarded whereas of the 85 babies with a normal outcome 70% were growth retarded.

Severe proteinuria. The adverse prognostic significance of severe maternal proteinuria was confirmed; that of duration of significant proteinuria was not. Severe proteinuria was associated with 19 (90%) of the pregnancies resulting in a poor outcome and in only 49 (58%) of the pregnancies with a good neonatal outcome.

Intraventricular haemorrhage. It was clear that serious degrees of intraventricular haemorrhage, diagnosed in the newborn by ultrasound scans, were a major adverse factor in newborn prognosis (Table 4). Of the 19 liveborn babies who had a poor outcome, 11 (58%) had serious degrees of intraventricular haemorrhage; the corresponding number in babies with a normal outcome was 16 out of 83 who had scans (19%). Apart from a clear relation (P <0·05) to early gestational age at delivery, the only antenatal factor isolated which might have some direct aetiological significance to intraventricular haemorrhage was duration of the maternal hypertension in the pregnancy (P <0·05).

Discussion

Severe hypertension presenting early in the second half of pregnancy is associated with

Table 3. Birthweight and outcome

Birthweight group (g)	No. of babies	Normal	Perinatal deaths	Late deaths	Severe handicap
500–999	27	15	7	4	1
1000–1499	53	46	4	1	2
1500–1999	25	23	2	—	—
2000–2499	1	1	—	—	—

Table 4. Neonatal cranial ultrasound findings

Grade*	Normal outcome	Poor outcome
Benign		
Normal	56	4
Germinal layer haemorrhage alone	5	1
Intraventricular haemorrhage I, IIa	5	3
Ventricular dilatation alone	1	0
Pathological		
Intraventricular haemorrhage IIb	0	2
Intraventricular haemorrhage III	0	2
Periventricular flares >48 h	16	3
Periventricular leukomalacia	0	3
Infarction	0	1
Not done	2	2†
Total	85	21

*Levene *et al.* (1985)
†Intrauterine deaths.

serious maternal and perinatal morbidity and mortality. The average obstetric unit in Great Britain or Ireland has limited experience in dealing with these patients. Because of this there has been inconsistency in management, and in recent reports on maternal mortality it was recommended that regionally based centres should be established for advice and management (Turnbull *et al.* 1986, 1989). This view has been generally endorsed by a study group of the Royal College of Obstetricians and Gynaecologists (Sharp & Symonds 1987).

Hammersmith Hospital has a considerable 'in-utero transfer' population which includes many of these patients with severe hypertension of onset in mid-pregnancy. In the past 8 years about 200 of these patients have required delivery before 34 weeks. During the last 5 years management has been consistent and under the personal direction of two of the authors (D.F.H. and M.G.E.). In an effort to improve management and thus the outcome in these preterm deliveries, we felt it important to determine which antepartum factors were primarily associated with a poor outcome and subject the associations to a stepwise regression analysis. We were looking not only for associations that would help in prognosis, but also for management factors with a primary relation to outcome which might call for modification in future management.

It was not surprising that the primary factor in a good outcome was the duration of pregnancy at delivery; or that intrauterine growth retardation and severe maternal proteinuria were adverse factors. The conditions requiring caesarean section as an emergency rather than electively are likely to be the main adverse factor rather than the procedure itself. Earlier elective delivery implies loss of fetal maturity and this could be more hazardous to the fetus than delivery as an emergency. Certainly, by controlling hypertension and gaining fetal maturity until there was a firm indication for delivery, we have not encountered the high perinatal mortality and major maternal complications reported by Sibai *et al.* (1985).

The finding that hypotensive episodes associated with the small bolus parenteral doses of hydralazine (5–10 mg) was associated with an adverse outcome suggests that diminution of placental perfusion is of primary importance in these patients. We still find it easier to manage hypertension with a basic regimen of methyldopa, rather than prolonged hydralazine infusions, but when hydralazine is needed to control exacerbations, we now give the drug by brief intravenous infusions.

The other aetiological factors usually thought to influence fetal outcome, such as maternal age, diagnosis and duration of hypertension, and the magnitude of the systolic and diastolic blood pressures reached seemed to be only of secondary importance in relation to fetal outcome.

A major degree of intraventricular haemorrhage has a primary influence on fetal outcome in these patients. Prevention is directly related to the gestational age achieved by the time of birth (Dunlop *et al.* 1986). There is some evidence that maternal steroid administration tends to reduce the frequency of intraventricular haemorrhage as well as that of respiratory distress syndrome (Lamont *et al.* 1983), and we have used these drugs freely. Pomerance *et al.* (1987) have reported that administration of vitamin K_1, 10 mg intramuscularly, to the mother at least 4 h before delivery reduces the occurrence of intraventricular haemorrhage, and we are planning a controlled trial on the use of this strategy.

Restriction of intravenous fluids to 1 litre plus output in the 24 h after delivery does no harm and is the only sure way, short of measuring the response of pulmonary wedge pressures to a fluid load, to avoid waterlogging oliguric patients with increased systemic vascular resistance and depressed ventricular function (Clark *et al.* 1986), a potentially lethal situation (Turnbull *et al.* 1989). Neither indwelling catheters nor use of frusemide in the first 24 h aid management, and the former add to patient discomfort and cause urinary tract infections. The only virtue of these procedures seems to be that they make the nurses and doctors feel they are doing something, and we do not use them.

The management protocol described for severe pregnancy hypertension seems to be justified by the results. With these patients with hypertension sufficiently severe as to require delivery between 26 and 34 weeks we have achieved an overall survival of 80% normal babies at 1 year of age. This was dependent on the quality of newborn paediatric care enabling us to deliver these babies when their chances of survival *in-utero* were small.

Comparison with other studies is difficult; on the one hand our sample of patients is heavily weighted by very severe cases transferred from other hospitals; on the other we have the benefit of excellent neonatal intensive care. A recent large study (Sibai *et al.* 1984) in Memphis reported a series of 303 patients with pre-eclampsia, arising *de novo* or in patients with essential hypertension. After correcting for lethal abnormalities they had a perinatal mortality in patients less than 33 weeks pregnant of 44%. When only similar patients in our series and 11 multiple pregnancies not included in the present analysis are considered, to make the studies comparable, we had a perinatal mortality of 18%.

We have established a management protocol for these patients with severe hypertension in pregnancy which is successful by current standards. The question still to be answered is whether or not results in the pregnancies with a 'poor outcome' can be improved further by establishing criteria for timing delivery in patients where there is any reasonable possibility of prolonging the pregnancy, against the background of our management. The problem is currently under study.

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Ultrasound and circulating placental protein measurements in complications of early pregnancy

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Summary. Maternal serum levels of human chorionic gonadotrophin (hCG), Schwangerschaftsprotein 1 (SP1) and pregnancy-associated plasma protein A (PAPP-A) were measured in an unselected group of 624 women presenting with amenorrhoea and vaginal bleeding with or without abdominal pain to an emergency gynaecological ultrasound clinic. Abdominal sector scanning was used to assess uterine contents. Pregnancy was confirmed by ultrasound in 406 pregnancies. Histological confirmation was obtained in each case of pregnancy failure. A live fetus was demonstrated in 259 women of whom six subsequently miscarried; one of these had markedly depressed serum hCG and PAPP-A, but normal SP1 levels, and two had oligohydramnios. Of the 147 women without ultrasound evidence of fetal heart action 67 had a correct ultrasound diagnosis of anembryonic pregnancy. The predictive value of a depressed serum hCG level was 70% in this group, and 31% in samples taken at ≤7 weeks. The predictive value of a normal hCG level was 96%. In 34 women missed miscarriage was diagnosed readily by ultrasound; all but five had depressed hCG and PAPP-A levels. A clinical diagnosis of a complete or incomplete miscarriage was made in 45 women and easily confirmed by ultrasound. All of them had depressed hCG, SP1 and PAPP-A levels. These results indicate that the diagnostic value of ultrasound in threatened miscarriage is often better than that of biochemical tests.

The triad of amenorrhoea, vaginal bleeding and abdominal pain leads to the greatest number of emergency admissions to gynaecological departments (Drumm 1981). The distinction between threatened, incomplete and complete miscarriage and ectopic pregnancy may be difficult clinically. Pelvic examination may permit an immediate diagnosis of evolving miscarriage if the cervix is dilated, or by the detection of other pathology; otherwise biophysical and biochemical tests should be used to exclude life-threatening conditions. Diagnostic ultrasound (abdominal or vaginal) will reliably detect intra-uterine fetal heart movements after 6 weeks amenorrhoea (Stabile *et al.* 1987), virtually ruling out ectopic pregnancy, although a proportion will nevertheless miscarry (Cashner *et al.* 1987). Westergaard *et al.* (1985) showed that if ultrasound results are not considered in women with classical symptoms and signs of threatened

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Table 1. Clinical outcome in 406 women with threatened miscarriage

	n	%
Live fetus *in utero*	259	63·7
Normal progress until 20 weeks	227	55·9
Elective termination of pregnancy	26	6·4
Subsequent miscarriage	6	1·5
Failed intrauterine pregnancy	147	36·2
Anembryonic pregnancy	67	16·5
Missed miscarriage	34	8·4
Hydatidiform mole	1	0·2
Incomplete miscarriage	41	10·1
Complete miscarriage	4	1·0

miscarriage, all biochemical indices studied [alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG), human placental lactogen (hPL), pregnancy-associated plasma protein A (PAPP-A), oestradiol (E_2), progesterone (P), and pregnancy zone protein (PZP)] are of equal value (predictive value positive 60–86%, predictive value negative 60–90%) in the prediction of subsequent miscarriage. If fetal viability is confirmed by ultrasound at the time of venepuncture, the positive predictive value (49%), sensitivity (89%) and relative risk (41%) of miscarriage is highest in women with depressed serum PAPP-A levels. Ultrasound features, such as intrauterine haematomata, fetal growth delay and a low-lying placenta have been described in women with threatened miscarriage. These features, together with bleeding for ≥3 days, have been reported to increase significantly the risk of miscarriage (Mantoni 1985).

Anembryonic pregnancy is the most common identifiable pathology in the first trimester (Fukijura *et al.* 1966) and is diagnosed by the absence of sonographic evidence of fetal or embryonic parts independent of the menstrual cycle or clinical data (Robinson 1975*a*). Other typical sonographic features include an irregular, poorly defined gestational sac which is small for gestational age (Nyberg *et al.* 1986). The predictive value of circulating trophoblastic and ovarian hormones and proteins in threatened miscarriage has been investigated in heterogeneous cohorts of women, many of whom had already miscarried, and no attempt was made to distinguish between the various causes of pregnancy failure (Salem *et al.* 1984; Masson *et al.* 1983). Yovich *et al.* (1986) demonstrated depressed circulating hCG levels as early as the 4th week after the last menstrual period in 16 subfertile women with anembryonic pregnancies who conceived after ovulation induction. Similar findings have been reported in spontaneous conceptions (Chapman *et al.* 1984). A missed miscarriage can be diagnosed by the sonographic absence of the fetal heart action in the presence of fetal parts (Robinson 1975*b*), relegating histological examination of the tissues of conception to establish the cause of pregnancy failure (Benirschke 1966). Morphological examination of the products of conception reveals externally normal embryos in 23% (Sentrakul & Potter 1966) to 48% (Creasy *et al.* 1976), and disorganized fetal parts in 1% (Fukijura *et al.* 1966) to 7% (Brotherton & Craft 1972) of miscarriages. In a prospective study Westergaard *et al.* (1985) showed that if repeated ultrasound failed to demonstrate fetal heart action there was little to choose between the measurement of fetal (AFP), ovarian (E_2, P), or placental hormones and proteins (hCG, SP1, PAPP-A), as levels were invariably low.

We have studied 624 consecutive unselected women with threatened miscarriage or suspected ectopic pregnancy attending an emergency gynaecological ultrasound clinic, in whom we assessed the diagnostic value of circulating levels of pregnancy-associated proteins (hCG, SP1 and PAPP-A) in conjunction with high-resolution abdominal sector scanning.

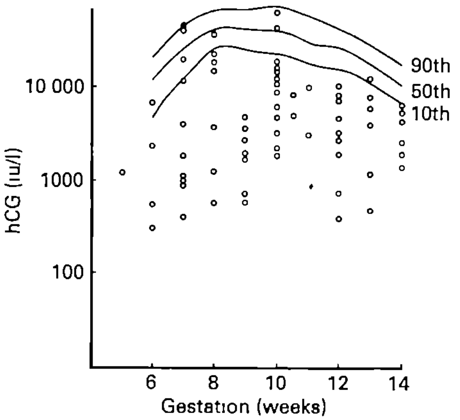

Fig. 1. Human chorionic gonadotrophin (hCG) measurements in 67 patients with anembryonic pregnancy at 5–14 weeks gestation (O), superimposed on the normal range (10th, 50th and 90th centiles determined from 488 samples in 227 patients with threatened miscarriage and normal outcome of pregnancy)

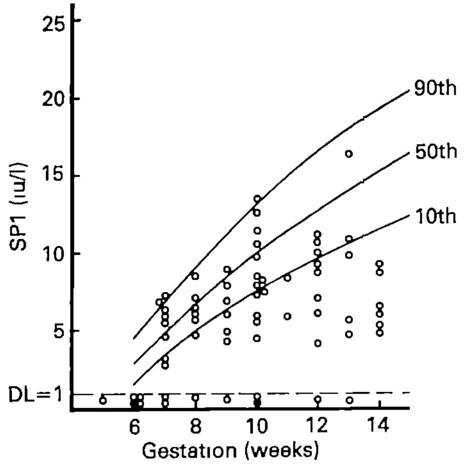

Fig. 2. Schwangerschaftsprotein 1 (SP1) measurements in 67 women with anembryonic pregnancy (O) superimposed on the normal range derived as for hCG in Fig. 1 DL, Detection limit of assay.

Subjects and methods

During an 18-month period, 624 women with amenorrhoea and vaginal bleeding, with or without abdominal pain, were recruited consecutively into a prospective study, as described previously (Stabile *et al.* 1987). The diagnosis was confirmed histologically on each occasion.

Ultrasound measurements

All the ultrasound examinations were made by the principal investigator using a sector scanner (Diasonics DRF100) through a full bladder, within 24 h of presentation to the casualty department. All the patients were followed up after their initial ultrasound visit to ascertain the clinical outcome. Subsequent miscarriage of a live fetus was diagnosed retrospectively.

If fetal heart movement was not detected then the following groups of pregnancy failure were described.

(a) An anembryonic pregnancy was diagnosed when there was an empty gestational sac of ≥3 ml in volume at ≥7 weeks gestation (with certain dates). If menstrual dates were uncertain, or the sac volume was <2·5 ml, a second examination was made a week later to confirm this diagnosis.

(b) A missed miscarriage was diagnosed when fetal parts were clearly demonstrated but no fetal heart action was present. If the fetal structure was deformed due to absorption, this condition was difficult to distinguish from a hydatidiform mole.

(c) The appearance of thick irregular echoes in the midline of the uterine cavity suggested an incomplete miscarriage. This was confirmed retrospectively by histological examination of the products of conception after evacuation of the uterine contents (Stabile *et al.* 1987).

The presence of a second empty gestational sac, intrauterine haematoma, oligohydramnios or other abnormal findings was noted. Measurements of maximal placental thickness and uterine area were obtained as described previously (Stabile 1988). After the initial assessment, gestational sac volume and crown–rump length were measured at weekly intervals if bleeding continued until 20 weeks gestation. Only one measurement per fetus at each week of gestation (at least 20 observations each week) were used to construct nomograms.

Biochemical measurements

Maternal venous blood (10 ml in a plain bottle) was obtained at the time of each ultrasound examination. Serum was separated within 2 h of collection and stored at −20°C.

Maternal serum levels of SP1 and PAPP-A were measured by radioimmunoassay as described previously (Sinosich *et al.* 1982; Grudzinskas *et al.* 1977). hCG was measured

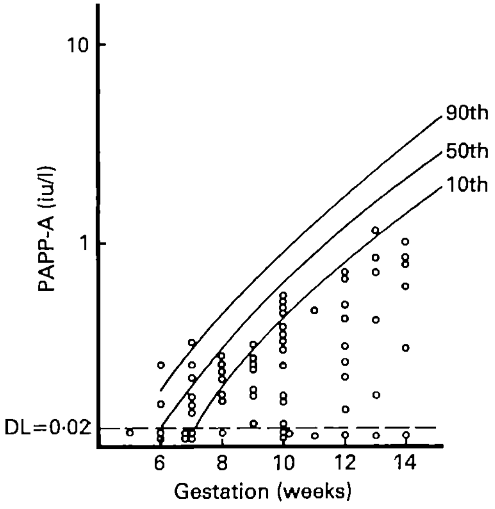

Fig. 3. PAPP-A measurements in 67 women with anembryonic pregnancy (O) superimposed on the normal range derived as for hCG in Fig. 1.

Table 2. Circulating human chorionic gonadotrophin (hCG), Schwangerschaftsprotein 1 (SP1) and PAPP-A in the prediction of anembryonic pregnancy (n=67)

	Sensitivity (%)	Specificity (%)	PV pos (%)	PV neg (%)
Depressed but detectable hCG	85·2	90·3	70·2	95·8
Depressed but detectable SP1	50·0	90·3	55·1	88·2
Depressed but detectable PAPP-A	65·4	90·3	60·7	91·9

using a commercially available kit (Amerlex-M hCG RIA, Amersham, UK).

The within- and between-assay coefficients of variation were always <10%. All the protein estimations were performed retrospectively by the principal investigator and were not available to the clinicians who managed all the patients based on the clinical and ultrasound data.

To provide a normal range for biochemical variables from 6 to 20 weeks gestation, 488 samples were obtained from the 227 women with threatened miscarriage whose pregnancies proceeded uneventfully until at least 20 weeks gestation. The mean number of observations at each gestational age week was 35 (range 26–44), and a maximum of three observations per patient were utilized.

Statistical methods

The clinical, ultrasound and biochemical data were analysed using the Statistical Package for Social Sciences. For each substance measured the results were divided into four groups: true positive (TP), false positive (FP), true negative (TN) and false negative (FN). For each type of pregnancy failure the following four diagnostic test parameters were calculated: the sensitivity (TP/TP+FN); the specificity (TN/FP+TN); the predictive value of an abnormal result (PV pos) (TP/TP+FP); the predictive value of a normal result (PV neg) (TN/TN+FN). It should be emphasized that the specificity is related to the composition of the control group who formed the basis for the normal range. In addition, the predictive value depends upon the ratio of affected to non-affected patients in the investigated group and is only generally applicable if the investigated population is a representative sample of the whole. Student's t-test was applied to assess the statistical significance of differences between study groups.

Results

Clinical

The final clinical diagnosis for each of the 624 women has been reported by Stabile *et al.* (1987). Pregnancy was confirmed by ultrasound in 406 women with threatened miscarriage (Table 1), all of whom had circulating hCG levels >25 iu/l. A live fetus of appropriate size was identified in 259 of these 406 women of whom 26 (10%) elected to terminate their pregnancy. In 227 of the remaining 233 women (97·4%) pregnancy proceeded uneventfully beyond 20 weeks.

Only six of the 259 women with a live fetus subsequently miscarried; the distribution of gestational age at first presentation was one each at 7 and 8 weeks and two each at 12 and 16 weeks. Mean age of the six women was 30·4 years (SD 7·6); 75% had had one or more pregnancies beyond 28 weeks and one or more miscarriages (mean 2·3). The first bleeding episode was significantly longer in these six women (mean 19·6, SD 26·7 days) than in those women with normal pregnancy outcome (mean 2·8, SD 1·4 days; $P<0{\cdot}001$).

Table 3. Circulating human chorionic gonadotrophin (hCG) and Schwangerschaftsprotein 1 (SP1) in the prediction of anembryonic pregnancy before 7 weeks gestation (n=15)

	Sensitivity (%)	PV pos (%)	PV neg (%)
Depressed but detectable hCG	66·7	31·3	97.6
Depressed or absent SP1	60·0	29·0	97·2

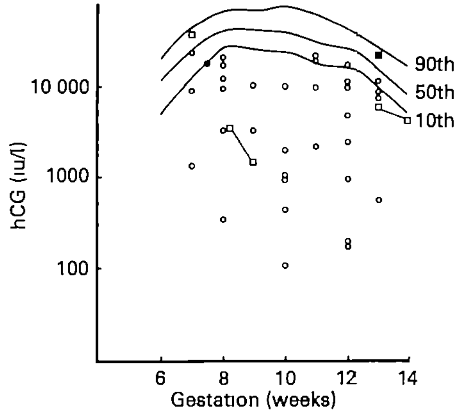

Fig. 4. Human chorionic gonadotrophin (hCG) measurements in 34 patients with a missed miscarriage (○) at 7–13 weeks gestation and four women who miscarried with (■) and without (□) oligohydramnios superimposed on the normal range derived as for hCG in Fig. 1.

Of the 147 women without fetal heart action at presentation 67 (45%) had a diagnosis of anembryonic pregnancy. The proportion of women with this diagnosis varied from 12% at 8 weeks to 37% at 10 weeks. The mean age at presentation in these patients was 27·3 (SD 7·2) years. The mean duration of the first bleeding episode was 5·2 (SD 4·7) days; 48% had bled for 1–3 days, 30% for 4–7 days, and 22% for 8–14 days before presentation. The mean gestational age at first presentation was 8 (SD 2·7) weeks. Of the women with a final diagnosis of an anembryonic pregnancy 47% had had one or more pregnancies which had progressed beyond 28 weeks, whereas 43% had had one or more miscarriages.

A fetal pole, albeit crumpled, was identified, without detection of fetal heart movements at the time of first presentation in 34 of the 406 (8%) women with threatened miscarriage. In two of these patients fetal heart movements had been clearly demonstrated the week preceding fetal death. Analysis of the fetal heart rate was not performed in these two patients. In another patient the diagnosis was missed as the appearance was indistinguishable from that of a hydatidiform mole. None of the patients who had a diagnosis of missed miscarriage was subsequently shown to have a continuing pregnancy. The mean age was 27·5 (SD 9·0) years; 33% had had one or more miscarriages and 50% one or more pregnancies continuing beyond 28 weeks. The mean gestational age at first bleeding episode was 10·7 (SD 2·5) weeks. In 80% of the patients the first bleeding episode lasted 1–3 days, and in the remaining women 4–7 days.

In all 41 women with incomplete miscarriage and the four with complete miscarriage, the diagnosis was made clinically and confirmed by ultrasound. Mean age was 25·6 (SD 7·2) years; 38% had had one or more previous pregnancies beyond 28 weeks, and 30% had had one or more miscarriages. Mean gestational age at first bleeding episode was 8·8 (SD 2·6) weeks. The first bleeding episode was longer in this group of women (mean 6·5, SD 4·9 days) than in women with normal outcome (mean 2·8, SD 1·3 days).

Ultrasound

The normal ranges for gestational sac volume and crown–rump length derived here were very similar to published nomograms of Robinson (1973, 1975*a*) which were obtained using a Compound B scanner, and are not shown here.

Of the six women who subsequently miscarried, ultrasound measurements of gestational sac volume were consistently small in the two women with oligohydramnios. Fetal measurements (crown–rump length) were normal in all six patients. Serial measurements of maximal placental thickness (results not shown) in these six women were consistently at the lower end of the normal range. Uterine area measurements were also not significantly different in pregnancies with normal and abnormal outcome (Stabile 1988).

In 52 of the 67 women with anembryonic pregnancies a positive diagnosis was made by ultrasound at first presentation because of the

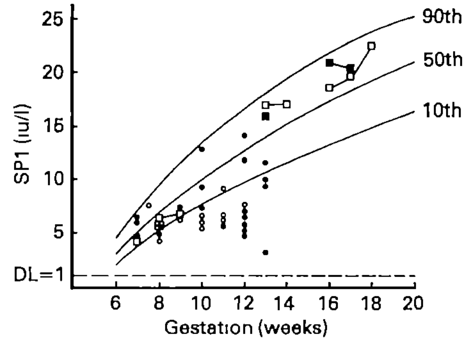

Fig. 5. Schwangerschaftsprotein 1 (SP1) measurements in 34 women with missed miscarriage (○) and six women who miscarried with (■) and without (□) oligohydramnios superimposed on the normal range derived as for hCG in Fig. 1.

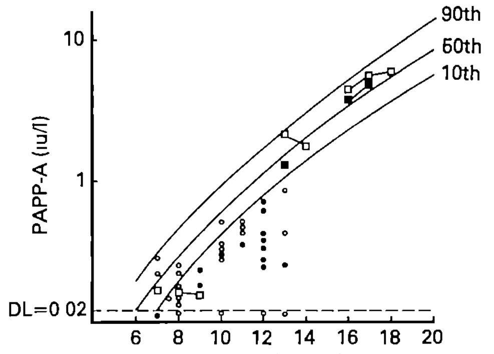

Fig. 6. PAPP-A measurements in 34 women with missed miscarriage (○) and six women who miscarried with (■) and without (□) oligohydramnios superimposed on the normal range derived as for hCG in Fig. 1.

absence of a fetal pole in a gestational sac >3·0 ml in volume. In the remaining 15 women a repeat examination, considered necessary because the gestational sac volume was <2·5 ml, confirmed the diagnosis a week later.

A missed miscarriage was diagnosed ultrasonically in 11% of patients presenting with painless vaginal bleeding at 7 weeks gestation, 9% at 8 weeks, 10% at 10 weeks, 26% at 12 weeks, and 17% at 14 weeks gestation. Measurements of maximal placental thickness and uterine area in this group of women were indistinguishable from those in women with other subgroups of pregnancy failure (results not shown). There were no other distinguishing ultrasound features in this group; in particular, no patient had a second empty gestational sac, intrauterine haematoma or oligohydramnios. Passive motion of the fetus in response to percussion was noted in two patients.

Complete and incomplete miscarriage was identified in 14% of patients presenting at 7–8 weeks, 31% at 10 weeks, 36% at 11 weeks and 5% at 12 weeks.

Biochemical

Figure 1 depicts the serum hCG levels in the 67 patients with anembryonic pregnancy presenting between 5 and 14 weeks gestation; 58 (86%) had a depressed (<10th centile) hCG level at the time of their first ultrasound scan. Their serum SP1 and PAPP-A levels are shown in Figs 2 and 3, respectively. Depressed or undetectable SP1 levels were present in 40 (60%), and 59 (88%) had depressed or undetectable PAPP-A levels.

Table 2 summarizes the test performance of each of the pregnancy proteins in the prediction of anembryonic pregnancy. The predictive value of an abnormal result was best for hCG (70%). A normal hCG result had a 96% probability (PV negative) of excluding this condition. Similar values were obtained for SP1 (88%) and PAPP-A (92%).

Table 3 analyses the prognostic value of biochemical tests in the diagnosis of anembryonic pregnancy at or before 7 weeks gestation. The sensitivity and predictive value positive of a depressed but detectable hCG level were 66% and 31% respectively while a normal result had a 98% chance of excluding this condition.

Of the six women with a live fetus who subsequently miscarried, four had hCG estimated in the first trimester (Fig. 4); the other two were scanned and sampled after 16 weeks. Two women had depressed hCG levels and it is remarkable that they both miscarried a few hours after the blood sample was taken. All the six women had normal SP1 levels (Fig. 5) including the two with oligohydramnios noted at ultrasound. PAPP-A levels (Fig. 6) were normal in all but one patient (who also had low hCG levels) and falling levels were noted in one other patient. These patients miscarried a few hours

Table 4. Sensitivity, predictive value (positive: PV pos; negative: PV neg) of single measurements of serum hCG, SP1 and PAPP-A in 34 women with missed miscarriage at the time of presentation (hCG, SP1) or after 7 weeks gestation (PAPP-A)

	Sensitivity (%)	PV pos (%)	PV neg (%)
Depressed but detectable hCG	85·3	56·9	97·6
Depressed but detectable SP1	55·9	46·3	93·2
Depressed but detectable PAPP-A*	82·8	52·2	97·6

*After 7 weeks amenorrhoea.

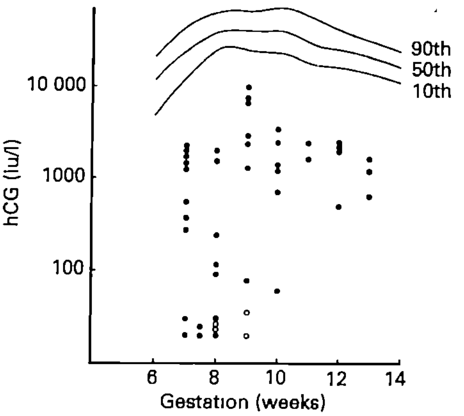

Fig. 7. hCG measurements in 41 women with an incomplete miscarriage (●) and four women with a complete miscarriage (○) superimposed on the normal range derived as for hCG in Fig 1.

after the scan had demonstrated a live fetus. The time interval between the final blood sample and scan and miscarriage ranged from 2 to 10 weeks in the remaining four patients, each of them had normal PAPP-A, SP1 and hCG levels. Thus, a normal level of any of these pregnancy proteins had a 97–99% probability of excluding subsequent miscarriage.

Circulating levels of hCG, SP1 and PAPP-A in 34 women with missed miscarriage are also shown in Figs 4–6 in relation to the 10th, 50th and 90th centiles of the normal ranges. All but five patients had depressed levels of hCG (<10th centile), but the values were always above 100 iu/l at the time of presentation. Similar findings were observed with respect to PAPP-A levels, whereas only 19 of the 34 patients (56%) had depressed SP1 values. Table 4 summarizes the sensitivity and predictive value positive and negative of each of the pregnancy proteins in the diagnosis of missed miscarriage, the statistical predictors being similar, but highest for hCG measurements. Circulating levels of hCG, SP1 and PAPP-A in the 45 women with complete and incomplete miscarriage are depicted in Figs 7–9, in relation to the 10th, 50th and 90th centiles of the normal ranges. All patients had depressed (<10th centile) but detectable levels of hCG. Similar findings were observed with respect to PAPP-A, whereas 7 (20%) had normal circulating SP1 levels. Table 5 summarizes the sensitivity and predictive value positive and negative of each of the pregnancy proteins in the diagnosis of complete and incomplete miscarriage, the statistical predictors being highest for hCG measurements.

Discussion

Our findings have highlighted the rarity of miscarriage after ultrasound demonstration of a live fetus in threatened miscarriage. These data confirm earlier reports (Wilson *et al.* 1986; Cashner *et al.* 1987).

Two of the six women who miscarried after a live fetus had been seen were noted to have oligohydramnios at 13 and 16 weeks gestation; they miscarried at 23 and 25 weeks respectively. Three previous reports (Robinson 1975*b*; Mantoni 1985; Chow & Vengadasalam 1986) have described this rare abnormality, and have implicated maternal infection with cytomegalovirus. In contrast to the series described by Westergaard *et al.* (1985) all but one of the six women had normal PAPP-A levels and only two of the six miscarried within hours of the last ultrasound scan. One of the two women had markedly depressed PAPP-A levels and in the other the levels had dropped from the 90th centile to below the 50th centile. In the remaining four women no information was available in the interval between the last observation and miscarriage (2–10 weeks). There was no evidence of maceration and the crown–rump length was compatible with the period of amenorrhoea in each patient. Two patients had sonographic evidence of

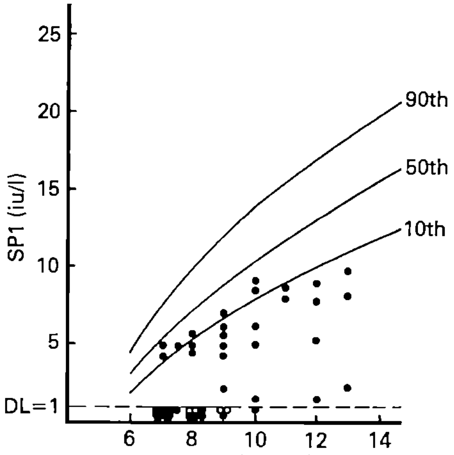

Fig. 8. SP1 measurements in 41 women with incomplete miscarriage (●) and four women with complete miscarriage (○) superimposed on the normal range derived as for hCG in Fig. 1.

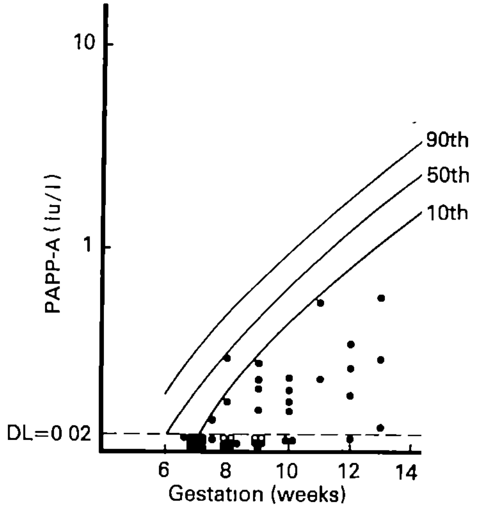

Fig. 9. PAPP-A measurements in 41 women with incomplete miscarriage (●) and four women with complete miscarriage (○) superimposed on the normal range derived as for hCG in Fig. 1.

oligohydramnios, and they miscarried 8 and 10 weeks after the last scan.

Normal serum hCG, SP1 and PAPP-A levels in the presence of fetal life are associated with normal pregnancy outcome in 97–98% of patients, in accordance with Westergaard *et al.* (1985). The present study has demonstrated that when detailed ultrasound and pregnancy protein results are considered together in women with threatened miscarriage, oligohydramnios is the only feature that consistently predicts an unsatisfactory outcome. Pregnancy protein levels were normal in the two patients with oligohydramnios, suggesting that the pathophysiology of this condition is independent of protein and hormone synthesis by the trophoblast.

Previous pathological studies have estimated that an intact empty gestational sac is found in 5–10% of miscarriages (Mikamo 1970). Many miscarriages, however, yield ruptured or incomplete sacs, such that the true frequency of anembyronic pregnancy is difficult to assess. The rate will also vary with differing clinical management policies such as the timing of curettage. We have found that anembryonic pregnancy was the commonest single underlying pathology in women with threatened miscarriage, occurring in 45% of those women whose pregnancy had already failed at the time of clinical presentation to hospital. Because this is a prospective ultrasound-based study we believe the rate expressed here is likely to be more accurate than pathological estimates.

It has previously been reported (Robinson 1975*a*), that given accurate knowledge of the menstrual dates, it is possible to diagnose all cases of anembryonic pregnancy at or after 7 weeks, when the sac volume is ≥3·0 ml. The possibility of a false positive diagnosis of this condition can be avoided by ignoring the menstrual history and considering only the sonographic criteria. Nonetheless, poor scanning conditions, including operator inexperience or the use of an inappropriate transducer, especially with a retroverted uterus, could increase the need for a repeat ultrasound examination. The increased resolution of the images obtained using vaginal sonography may overcome limitations due to patient obesity and an inadequately filled bladder. The present study confirms the findings of Robinson (1975*b*), although a repeat ultrasound examination was necessary in 15 patients with anembryonic pregnancy. The addition of a single hCG or SP1 estimation in these women would have provided the clinician with additional information in that normal levels of these proteins are associated with a 97% chance of excluding an anembryonic pregnancy. However, the positive predictive value of depressed hCG (67%) and SP1 (46%) is too low to be of practical clinical value. In addition, since PAPP-A cannot be reliably and con-

Table 5. Sensitivity, predictive value (positive: PV pos; negative. PV neg) of single measurements of serum hCG, SP1 and PAPP-A in 45 women with the diagnosis of complete or incomplete miscarriage

	Sensitivity (%)	PV pos (%)	PV neg (%)
Depressed but detectable hCG	100	67·2	100
Depressed but detectable SP1	73·1	46·3	96·7
Depressed but detectable PAPP-A*	94·7	45	99·5

*After 7 weeks amenorrhoea.

sistently measured in the peripheral circulation before 7 weeks gestation, it would provide no additional information in this situation. Our findings show that ultrasound can reliably diagnose anembryonic pregnancy when circulating hCG, SP1 and PAPP-A levels are not consistently depressed, which would imply that, at least in early pregnancy, trophoblastic production of these proteins is not dependent on the presence of an embryo or fetus.

In this series, missed miscarriage was diagnosed in 8% of patients presenting with painless vaginal bleeding in early pregnancy. This is considerably lower than reported by others (Robinson 1975*b*: 39% of the study group; Mantoni 1985: 15% of the study group), and may be due to the design of our study with the recruitment of unselected consecutive patients with sonographic and biochemical evidence of pregnancy presenting with symptoms and signs of threatened miscarriage in the first trimester. Furthermore, histological confirmation of this diagnosis was obtained in each patient.

In the only two pregnancies in which a live fetus had been noted in the week preceding fetal death, circulating levels of hCG, SP1 and PAPP-A were all normal at first presentation. These observations do not support the view that depressed levels would be expected before the fetus dies, our findings suggesting that depressed levels may follow rather than precede fetal death in some patients. With respect to hCG levels our results would imply that the trophoblast may continue to synthesize this hormone for some time after fetal death. In addition, caution should be exercised if, in the absence of ultrasound facilities, a positive urinary or serum pregnancy test (with a detection limit of 100 iu/l hCG) is found, as this cannot be taken as evidence of fetal life. We would conclude that the value of ultrasound examination surpasses that of any of the biochemical tests we have studied in the diagnosis of a missed miscarriage. The occasional difficulty in distinguishing a hydatidiform mole from a long-standing missed miscarriage, and *vice versa*, is not a clinical problem, as the pregnancy can confidently be described as having failed. If ultrasound findings are ambiguous, hCG estimations should be used to discriminate between these two conditions. The ease with which ultrasound can confidently diagnose fetal life renders it the ideal investigation in a woman with symptoms and signs of threatened miscarriage. Our results confirm that if ultrasound is available, then the diagnosis of a missed miscarriage is not improved by any of the biochemical tests we have studied.

A single ultrasound examination correctly diagnosed complete and incomplete miscarriage in all the 45 women studied. However, it must be emphasized that organized blood clots may look similar to retained placental tissue, both giving the appearance of thick, irregular echoes in the midline of the uterine cavity (Campbell 1972; Robinson 1972). Complete miscarriage was diagnosed in only 1% of the women presenting with threatened miscarriage. In these four women the principal investigator excluded the presence of retained products, because a regular and clearly defined endometrial line was seen ultrasonically. None of these women required curettage after presentation, normal menstruation returning within a few weeks.

Our findings with respect to the low circulating pregnancy protein levels in complete and incomplete miscarriage are consistent with failure of pregnancy. The depressed levels were most likely due to the slow clearance rates from the circulation [the half-lives being: hCG 48 h (Barnea & DeCherney 1986); SP1 20–40 h (Menabawey *et al.* 1979); and PAPP-A 3 days (Smith *et al.* 1979)] and may not be a true reflection of the condition of the trophoblast at the time of sampling. It is also possible that remnants of trophoblastic tissue may remain viable for a variable time after expulsion of the fetus, such that single estimations are of little help to the clinician. In this study, ultrasound examination correctly identified all the women with retained products of conception, allowing prompt evacuation of the uterus. By contrast, the value of ultrasound examination in the diagnosis of complete miscarriage awaits a larger study. We would conclude that the measurement of any of the pregnancy proteins studied here does not provide additional information to influence the clinical management and merely reflects the slow clearance of placental products from the maternal circulation.

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A study of the experience of Glasgow women in the climacteric years

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Summary. Overall, 424 women between 40 and 60 years of age were interviewed with reference to their experience of the menopause; 179 (42%) expressed a 'need for treatment' which was more marked in those who had had a hysterectomy (57%) or oophorectomy (76%). Of those who sought help (174) a large majority (92%) had seen their general practitioner and 72% received some form of drug therapy, predominantly hormone replacement therapy (HRT) or psychotropic drugs. Twenty-eight women were currently having HRT (7%) and 39 (9%) had previously had HRT. Only 12 women (3%) had received >3 years of HRT and nine of these had had an oophorectomy. Only 1% of other women were 'long-term' users of HRT. Of the 424 women 11% expressed dissatisfaction with their general practitioner's approach to this subject.

In mid-life women face the climacteric transition in addition to the physical and social changes experienced by both sexes during the same years. Some women become distressed by menopausal symptoms (Neugarten & Kraines 1965; McKinley & Jeffreys 1974; Thompson *et al.* 1973; James *et al.* 1984) but many are relatively untroubled. Much research on the menopause is stimulated by menopause clinic specialists, and our view of climacteric problems may be biased by the nature of the specialist clinic population since this may include a disproportionate number of women (i) with particularly difficult problems, (ii) on long-term hormone replacement therapy (HRT) after hysterectomy, and (iii) whose request for help has not met with a sympathetic response elsewhere. In a careful community study, Bungay *et al.* (1980) reported some symptoms to be as common in men as in women in mid-life but there were menopause-associated peak prevalences for flushing (50%), night sweating (30%) and loss of confidence (30%).

The present study set out to examine climacteric experience by a survey of women in our community in order to clarify our potentially distorted menopause clinic viewpoint. Since the enquiry examined the interaction of these women with health care we wished to ensure a diversity of general practices whereas many previous studies directed at symptom frequency have, appropriately, limited their survey populations to one or a few general practices (McKinley & Jeffreys 1974; Thompson *et al.* 1973; Gath *et al.* 1987; Bungay *et al.* 1980). We judged that a study of women employed in some city centre venues would ensure a wide spread of different general practitioners from the Glasgow area.

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Table 1. Classification of study population by age and menstrual status

Menstrual status	Age groups (years) 40–44	45–49	50–54	55–59	All
Premenopausal	71	73	29	2	175 (41·3%)
Postmenopausal	3	24	72	89	188 (44·3%)
Hysterectomy	5	9	10	4	28 (6·6%)
Oophorectomy	6	8	9	10	33 (7·8%)
Total	85 (20·0%)	114 (26·9%)	120 (28·3%)	105 (24·8%)	424 (100%) (100%)

χ^2-test $P<$ 0·001

Subjects and methods

The survey included 424 women in the age range 40–60 years. Permission was obtained to approach them at their place of work to provide a brief confidential interview. The women were asked about their health experiences of mid-life and all but 14 of the women approached agreed to be interviewed. The women were employees in two large Glasgow department stores (*n* = 73) and in four Glasgow hospitals (*n* = 351), in the nursing (*n* = 159), catering (*n* = 23) and domestic (*n* = 169) services. Women who had had at least one menstrual period within 6 months of being interviewed were classified as premenopausal. Those with no period for ≥6 months were considered to be postmenopausal.

The interviews were conducted by a single interviewer and generally took place during work tea-breaks. A standard questionnaire was administered and responses classified by the interviewer. Social class data were based on husband's occupation for married women and by their own occupation status for the others. A self-administered symptom questionnaire was also completed. The survey was carried out during summer 1983.

Results

The mean age of the 424 women in the study was 50·0 (SD 5·6) years; 249 (59%) were no longer menstruating, the mean time since the last menstrual period was 5 years (median 2 years). The distribution by age and menstrual status is shown in Table 1. Their marital status was: currently married 328 (77%); single 34 (8%); separated or divorced 23 (5%) and widowed 39 (9%). All the women were in paid employment and 283 (86%) of the women's partners were also in work; the remainder being retired, disabled or unemployed. The social class distribution was: classes I and II 84 (20%); class III 169 (40%); classes IV and V 100 (24%) and unknown 71 (17%).

Table 2. Contraceptive use in 175 premenopausal women

Contraception	Age groups (years) 40–44 (*n*=71) (%)	45–49 (*n*=73) (%)	50–54 (*n*=29) (%)	55–59 (*n*=2) (%)	All (*n*=175) (%)
Nil	56·3	64·4	75·9	100	63·4
Sterilized	18·3	19·2	13·8	—	17·8
Vasectomy	2·8	—	—	—	1·1
Combined pill	8·5	6·8	3·4	—	6·9
Progestogen	1·4	—	—	—	0·6
IUCD	11·3	2·7	—	—	5·7
Cap	1·4	—	3·4	—	1·1
Sheath	—	2·7	3·4	—	1·7
Other	—	4·1	—	—	1·7

IUCD, Intrauterine contraceptive device.

Table 3. Menstrual status and subjective 'need for treatment' for menopausal problems at any time in women 40–59 years

	Need for treatment for menopausal problems at any time	
Menstrual status	No *n* (%)	Yes *n* (%)
Premenopausal	116 (66·3)	59 (33·7)
Postmenopausal	109 (58·0)	79 (42·0)
Hysterectomy	12 (42·9)	16 (57·1)
Oophorectomy	8 (24·2)	25 (75·8)
Total	245 (57·8)	179 (42·2)

χ^2-test $P < 0{\cdot}001$.

Their climacteric experience and interaction with health care services are detailed as follows.

Current contraception

There were 175 premenopausal women in the study. Their use of contraception analysed by age groups is presented in Table 2. At all age bands within this group a majority employed no contraception (63% overall). Sterilization was the most frequently employed method of preventing pregnancy (19% of women), and usually involved female sterilization (94% of sterilizations). The proportion involving vasectomy is so low that it is possible that the question failed to detect all of them. The combined oral contraceptive pill and the IUCD were the most frequently used reversible methods but were rarely used after 49 years of age.

Subjective need for treatment

When asked if they had ever felt 'in need of treatment for the menopause', 179 women (42%) expressed having felt such a need. The age at which the women first felt a 'need for treatment' was also recorded. At the time when the 'need for help' was first noted, 53% were premenopausal and 24% were postmenopausal. The remaining 23% had had a hysterectomy. A significantly greater proportion of those who had had a hysterectomy considered that they 'needed treatment' (Table 3); 75% of the oophorectomized women and 57% of those who had had a hysterectomy only 'needed treatment'. The women often mentioned more than one symptom as their reason for perceiving a need for treatment but 69 women mentioned vasomotor symptoms alone and 18 psychological symptoms only. Overall, 121 (68%) of the women who considered that they had needed treatment mentioned vasomotor symptoms, 76 (43%) mentioned psychological symptoms, and 47 (26%) tiredness. The numerous other symptoms mentioned were less frequently represented and included headaches, vaginitis, sexual disorders and fluid retention.

Experience of health care

Overall, 174 women (41%) had actually sought help, and of these, 160 (92%) consulted their general practitioner, six consulted a gynaecologist direct and the other eight women consulted nurses, physicians or family planning services. The outcome of these consultations was that 107 women (62%) received a form of drug treatment, 35 (20%) received reassurance, 15 women (9%) felt their problem was disregarded, 11 women (6%) were referred to hospital clinics, and for 6 (3%) the result is unknown. Of the referrals, five were to a menopause clinic, four to a psychiatrist and the remainder to a gynaecologist or physician.

Use of drug therapy

Overall, 125 women received some form of drug therapy related to menopause problems at some time (29% of the total study population) and 60 were currently receiving drug treatment. Of the

Table 4. Use of drugs in the treatment of menopausal complaints

Drugs	Current	Past	Ever
HRT	28	37	65
HRT + psychotropic	—	2	2
Psychotropic drugs	17	14	31
Psychotropic + clonidine	1	—	1
Clonidine	3	2	5
Progestogen	2	—	2
Pyridoxine	2	—	2
Beta-blocker	1	—	1
Analgesics	2	1	3
Anti-emetics	1	—	1
Diuretics	2	1	3
Unidentified	1	8	9
Total	60	65	125

HRT, Hormone replacement therapy.

Table 5. Use of hormone replacement therapy (HRT) and psychotropic drugs by menstrual status

		HRT				Psychotropic drugs			
		Current		Past		Current		Past	
Menstrual status	*n*	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Premenopausal	175	9	(5·1)	6	(3·4)	6	(3·4)	6	(3·4)
Postmenopausal	188	7	(3·7)	22	(11·7)	8	(4·3)	9	(4·8)
Hysterectomy	28	3	(10·7)	5	(17·9)	1	(3·5)	—	—
Oophorectomy	33	9	(27·3)	6	(18·2)	2	(6·1)	1	(3·0)
Total	424	28	(6·6)	39	(9·2)	17	(4·0)	16	(3·8)

65 women no longer receiving treatment 74% were still symptomatic and overall 153 women were currently symptomatic. The most frequently used were HRT and psychotropic drugs such as antidepressants or tranquilizers (Table 4). Sixty-seven women (16%) had received HRT at some time with 28 (7%) currently using HRT. Thirty-four women (8%) had received psychotropic drugs at some time including 18 (4%) currently having treatment. Together these drugs were taken by 77% of the women currently on treatment. The use of these two treatment types by the different menstrual status groups is shown in Table 5. There was a significant increase over the other groups in current use of HRT in the hysterectomy and oophorectomy groups with no similar trend in the use of psychotropic drugs. Examination of the duration of therapy (Table 6) revealed that only 15% of past HRT treatment had been for ≥2 years but that current HRT treatment, so far, involved treatment for >2 years in 61% of women receiving HRT. Despite being a small group (8% of women overall) the women with no ovaries accounted for a large proportion of those currently on HRT for ≥2 years (47%) and they dominated all other groups in terms of treatment for >3 years (70%). Altogether 46% of the oophorectomized women had been on HRT at some time compared with 9%, 15% and 29% in the premenopausal, postmenopausal and hysterectomy groups respectively (Table 5).

Satisfaction with care provided

All the women were asked if they had formed an impression of the attitude of their general practitioners towards menopausal problems. Most had not formed an opinion but 165 did express a view: 92 (56%) felt that their doctor was very helpful and 28 (17%) that their doctor was minimally helpful. The remaining 45 women judged their general practitioner to be unhelpful. Thus only 11% of the total population expressed dis-

Table 6. Duration of hormone replacement therapy (HRT)

		Period of HRT use (years)					
Menstrual status	*n*	<2	2–3	4–7	8–11	12–15	Total
Current therapy							
Premenopausal	175	7	2	—	—	—	9
Postmenopausal	188	2	2	2	1	—	7
Hysterectomy	28	1	2	—	—	—	3
Oophorectomy	33	1	1	4	1	2	9
Total	424	11	7	6	2	2	28
Past therapy							
Premenopausal	175	6	—	—	—	—	6
Postmenopausal	188	21	1	—	—	—	22
Hysterectomy	28	2	3	—	—	—	5
Oophorectomy	33	4	—	1	1	—	6
Total	424	33	4	1	1	—	39

satisfaction with their doctor's approach to this field. A similar pattern of opinion was obtained in the subgroup of 126 women who received drug treatment.

Only 44 women (10%) in the study knew that there were menopause clinics in Glasgow; 16% of the nursing staff had a knowledge of these clinics compared with 9% of the catering staff, 2% of the domestic staff and 7% of the shop assistants.

Discussion

We recognize the potential danger of our study population being an unrepresentative sample of Glasgow women since our survey examined only employed women and is likely to miss those in poor physical or mental health. It is reassuring that the 1981 Census reports that Glasgow City women (40–59 years of age) have very similar marital status statistics to those in the present study (married 77 *vs* 74%; single 8 *vs* 11%; widowed 9 *vs* 10%; and divorced/separated 5 *vs* 5%, respectively. The Glasgow City class structure was reasonably similar to that in our study group (I–II 22 *vs* 20%; III 49 *vs* 40%; IV–V 29 *vs* 24%; with 17% unclassified in our survey). Another potential source of bias could be the use of hospital staff who might have a heightened awareness of the issues studied as a consequence of the presence of menopause clinics in the city's hospitals. The study suggests that only a small percentage of the women knew of the long-established clinics.

Although the symptom complex which makes up the menopausal syndrome has been studied by several authors, we have little information on the experience of health care services by women at the menopause. In a general study of 48 practices in England and Wales, the consultation rate for menopausal symptoms in 1 year was 88·2/1000 women at risk between 45 and 64 years which was one of the highest rates quoted for any category of complaint in that survey (Morbidity Statistics from General Practice 1981/82).

It is clear from the present work that most women who feel that they have a menopause problem do seek help and that the usual avenue is to consult their general practitioner. It is reassuring to see that most of these women (73%) felt that they met with a helpful response but 45 women (11% overall) were dissatisfied with their general practitioner's response to their enquiry. It is likely that women in this latter group are over-represented at menopause clinics, thus creating the impression that a larger proportion of general practitioners are unsympathetic to menopause problems. The nature of the general practitioner response was principally HRT, psychotropic drugs or reassurance and explanation. All of these responses would be appropriate, depending on the individual clinical picture, but it is of interest that where drug therapy was used this tended to be of relatively short duration despite the fact that most of those who had been taken off treatment (74%) were still symptomatic. Although most women receiving drug treatment received it in the form of HRT, a significant minority received psychotropic drugs. Psychological symptoms were commonly reported by the women and have been studied in depth by previous authors. The extent to which these are specifically related to the menopause remains controversial but Bungay *et al.* (1980) reported peaks of incidence of some minor psychological symptoms at the menopausal years and Gath *et al.* (1987) observed an association between psychiatric state and vasomotor symptoms in the 45–49-year age group. The latter study particularly noted an association between psychiatric symptoms and an increased likelihood that the woman would consult her general practitioner with menstrual problems. Skegg *et al.* (1977) reported that the highest rate of general practitioner prescriptions for psychotropic drugs was in the 45–49-year age group. This tendency was observed in the present study, with HRT and psychotropic drugs being the dominant forms of treatment used. We would argue that some of the women given psychotropic drugs could have been treated using oestrogen which can improve minor psychological symptoms (Campbell 1976).

Women undergoing hysterectomy and oophorectomy are known to show a high prevalence of menopause symptoms (Chakravarti *et al.* 1977) but despite this established information many such women in the present survey had not received prophylactic or early treatment to prevent problems. These groups reported higher rates of feeling in need of treatment in the survey. After oophorectomy, some women received HRT for several years and constituted the only group which did so. There was little evidence of women and their general practitioners opting for long-duration HRT. One group which might have been easily treated long term with HRT is the hysterectomy group since concerns about menstruation, progestogens and endometrial cancer are not relevant, but none of the 28 women in the hysterectomy group had received more than 3 years treatment. It is likely that both patient-related factors (dislike of menstruation, fear of 'hormones') and doctor-related factors (preference for patients coping with menopause, concern about long-term effects of oestrogen) are relevant to the non-use of long-term HRT.

The current media attention given to postmenopausal osteoporosis, including the publicity of the National Osteoporosis Society, occurred after this survey was conducted. This raises the possibility that these campaigns may have stimulated the use of longer-duration HRT and heightened patient awareness. Certainly the authors in their specialist clinics have noticed an increase in enquiries about osteoporosis prevention but it is not clear whether there has been a significant shift in perception in the community. At the time of the survey, concern about osteoporosis was not mentioned by these Glasgow women as a reason for feeling in need of treatment for the menopause.

The menopausal transition faces all women and many experience symptoms. Although a small number of menopause clinics exist and can research the development of safe and effective therapy and try to lead opinion in this field, the data presented demonstrate that even in a city with a relatively high number of menopause clinics (three hospital clinics) the contribution they can make to direct patient care is very small. It may be argued that optimal advice and treatment for menopause problems might be achieved by a significant growth in menopause clinics as has occurred with family planning clinics but in the present financial climate such a concept is unrealistic. The advice and treatment of most women requesting menopause-related help rests with general practitioners, thus it is of paramount importance that accurate and up-to-date information and guidance are effectively disseminated to help general practitioners meet the needs of climacteric women.

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Changes in the connective tissue of corpus and cervix uteri during ripening and labour in term pregnancy

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Summary. The composition of the connective tissue of human cervix and corpus uteri was studied in tissue specimens from seven non-pregnant women and 14 pregnant women, delivered at term by section, to examine spontaneous cervical ripening and labour-induced changes in both the uterine and the cervical connective tissue. The main finding in both the cervix and the corpus was a large (40–60%) decrease of the collagen concentration. The collagen extractability, obtained by pepsin digestion, was increased twofold, suggesting a change of the organization of the collagen fibrils. This reorganization process could also be demonstrated by a large increase of the collagenolytic activity demonstrated with an artificial DNP-peptide substrate. The concentrations of sulphated glycosaminoglycans was lower in pregnant women than in non-pregnant women. The results show that both the cervix and the corpus uteri contain substantial amounts of connective tissue components (collagen, sulphated glycosaminoglycans and hyaluronic acid) and that during ripening, reconstruction of the connective tissue components occurs in both sites. This indicates that the cervical state reflects that of the myometrium.

Previous investigations have shown that the human uterine cervix is dominated by connective tissue and that spontaneous cervical ripening at term involves profound changes in the organization and concentration of collagen, proteoglycans and hyaluronic acid (Uldbjerg *et al.* 1983*a*). Ripening of the cervix, namely softening and dilatation, signals the onset of labour and facilitates the subsequent delivery. Moreover, in late pregnancy the previously 'relaxed' myometrium shows increased activity characterized by prelabour-like uterine contractions.

Although the corpus uteri is dominated by smooth muscle, it also contains considerable amounts of connective tissue (Schwalm & Dubrauszky 1966). Since the cervix and the corpus uteri constitute a functional unit we thought it important to investigate whether a 'ripening' process, similar to that of the cervix, also takes place in the connective tissue of the corpus uteri.

Materials and methods

Tissue specimens from 21 women were obtained from the fundus, isthmus and cervix uteri, as described previously by Uldbjerg *et al.* (1983*a*).

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All patients consented to participate in the study which was approved by the local ethics committee of the Karolinska Hospital. Group A (controls) consisted of seven non-pregnant fertile women who were to undergo hysterectomy for non-malignant diseases such as meno-metrorrhagia, ovarian cysts, etc; group B consisted of seven pregnant women at term with unfavourable cervices who were to be delivered by elective caesarean section for cephalopelvic disproportion; and group C consisted of seven pregnant women at term with spontaneous onset and adequate progress of labour who had to be delivered by caesearean section due to signs of acute fetal distress (Table 1).

Biochemical analyses

Water and glycosaminoglycans. The water content of the biopsies was defined as the difference between the wet and the dry weight as described previously (Uldbjerg *et al.* 1983*a*). The concentrations of hyaluronic acid and sulphated glycosaminoglycans were determined as hexosamine concentration after drying, delipidation with acetone, papain digestion and purification on columns of DEAE-cellulose (Uldbjerg *et al.* 1983*b*; Antonpoulus *et al.* 1964).

Collagen concentration and extractability. The biopsies were cut into pieces <2 mm and delipidated with acetone. They were initially extracted three times with 1 ml 0·5 M acetic acid and then three times with 1 ml 0·5 M acetic acid containing pepsin (1 mg/ml). Extractions (23 h) and centrifugations (1 h at 20 000 *g*) between these procedures were performed at 4°C. The material was hydrolysed in 2 ml of 6 M HCl at 100°C for 17 h, lyophilized and estimated as hydroxyproline according to Stegeman & Stalder (1967).

Table 1. Clinical data for the three study groups: non-pregnant women (group A); pregnant women at term (group B); and women in labour (group C)

	Group A (n = 7)	Group B (n = 7)	Group C (n = 7)
Age (years)	45·8 (43–49)	31 (17–39)	31·4 (25–39)
Parity	1·6 (0–3)	1·1 (0–2)	0·2 (0–1)
Gestational age (weeks)	—	40·1 (37–43)	41 (40–42)
Cervical score (0–10)	—	2·5 (0–4)	—
Cervical dilatation (cm)	—	—	5·4 (3–7)
Day of cycle	10 (5–15)	—	—

Results are mean (range) values.

Collagenolytic activity. Extractions were essentially performed as described by Kitamura *et al.* (1980). The specimen was crushed by 10 tons pressure during cooling with liquid nitrogen and then homogenized in 13 volumes of 0·25% Triton X-100, 50 mM Tris, pH 7·3, containing 100 mM $CaCl_2$ in a TRI-R tissue homogenizer, S61, for 4 min at 3000 rev/min. The homogenate was centrifuged at 15 000 *g* for 20 min at 2°C, whereafter the supernatant was diluted with extraction buffer. The hydrolytic activity against DNP-peptide was then assayed as described by Masui *et al.* (1977). The incubation time was 2 h and the extraction buffer was used as blank. The activity was determined against a DNP-peptide (2,4-dinitrophenyl - Pro-Gln-Gly-Ile-Ala-Gly-Gln-D-Arg).

Chemical reagents. Papain (twice crystallized, 16–40 BAAE units/mg) was purchased from Sigma Chemical Co., USA, DEAE cellulose ion exchanger (DE-52) from Whatman Ltd, England, and 2,4-dinitrophenyl-Pro-Gln-Gly-Ile-Ala-Gly-Gln-D-Arg (DNP-peptide) from the Protein Research Foundation, Japan. All other chemicals were of analytical grade.

Statistical methods

One-way analysis of variance was used to test differences among group means. If the *F*-test was significant, Newman Keul's procedure was used for further comparisons.

For variables where variances were not homogeneous, Kruskal–Wallis one-way analysis of variance was used. Means were estimated together with their 95% confidence intervals. A significance level of 5% was used.

Results

Biospsies from the fundus, the isthmus and the cervix uteri were compared in non-pregnant women and in pregnant women before and during labour.

Non-pregnant women

The composition of the connective tissue at the three different locations differed. The concentration of collagen estimated as hydroxyproline was highest in the cervix (14·8 μg/mg w/w), somewhat lower in the isthmus and the fundus (Table 2). The amount of collagen solubilized by pepsin digestion varied considerably, being lowest in the cervix (33·3% of total collagen) and high in the fundus (62·5%) (Table 3). The collagenolytic activity measured as the activity against a DNP-peptide was low in all three locations (Table 4). The water concentration was similar to that in specimens from pregnant women (Table 5). The concentrations of sulphated glycosaminoglycans and hyaluronic acid were almost the same in the fundus, the isthmus and the cervix (Table 6).

Term pregnancy

The concentrations of collagen before labour were significantly lower in the fundus, the isthmus and the cervix uteri compared with values in the non-pregnant state. The decrease in collagen was greatest in the cervix resulting in similar collagen concentration at all three locations (Table 2). Not only the concentration but also the arrangement of collagen fibres changed during pregnancy. A significant increase in the percentage of collagen solubilized by pepsin digestion was noted (Table 3). The decreased concentration as well as the changed arrangement of the collagen was accompanied by an increase in the hydrolytic activity against the DNP-peptide in the cervix (Table 4). The water concentration did not differ significantly between biopsies from pregnant and those from non-pregnant women (Table 5). Compared with the non-pregnant state, the concentration of sulphated glycosaminoglycans measured as hex-

Table 2. Collagen concentration (determined as hydroxyproline) in cervical and uterine tissues from non-pregnant women (group A), pregnant women at term (group B) and women in active labour (group C)

	Hydroxyproline (μg/mg w/w)		
Tissue specimen	Group A ($n = 7$)	Group B ($n = 7$)	Group C ($n = 7$)
Fundus uteri	10·55 (9·19 to 11·90)	6·39* (4·82 to 7·95)	6·64* (5·07 to 8·20)
Isthmus uteri	14·20 (12·66 to 15·72)	6·62* (5·25 to 7·99)	6·23* (4·86 to 7·59)
Cervix uteri	14·80 (12·57 to 17·03)	5·56* (3·07 to 8·06)	6·43* (3·93 to 8·92)

* $P<0·05$.

Results are expressed as means with 95% confidence interval in parenthesis.

Table 3. Percentage of collagen in two extracts and remaining pellet in cervical and uterine tissues from non-pregnant women (group A), pregnant women at term (group B) and women in labour (group C)

Tissue specimen	Group A ($n = 7$)	Group B ($n = 7$)	Group C ($n = 7$)
Extractability in 0·5 M acetic acid (%)			
Fundus uteri	1·3 (0·5 to 2·2)	1·0 (0·1 to 2·0)	0·3 (−0·6 to 1·3)
Isthmus uteri	2·7 (1·1 to 4·2)	1·0 (−0·5 to 2·6)	0·6 (−1 to 2·1)
Cervix uteri	0·7 (0·4 to 1·1)	0·9 (0·5 to 1·2)	0·8 (0·4 to 1·2)
Extractability in 0·5 M acetic acid + 1 mg pepsin/ml (%)			
Fundus uteri	62·5 (42·9 to 81·9)	94·2* (93·4 to 95·0)	93·2* (87·3 to 99·1)
Isthmus uteri	48·2 (26·3 to 70·1)	92·4* (89·4 to 95·4)	94·9* (91·3 to 98·6)
Cervix uteri	33·3 (18·9 to 47·6)	85·8* (71·7 to 99·9)	92·3* (79·5 to 105·8)
Not extractable (pellet) (%)			
Fundus uteri	36·2 (15·7 to 56·6)	4·8* (2·0 to 7·5)	6·5* (0·9 to 12·0)
Isthmus uteri	49·1 (24·3 to 73·9)	6·6* (3·5 to 9·6)	4·5* (0·3 to 8·6)
Cervix uteri	66·0 (51·7 to 80·3)	13·3* (−0·7 to 27·3)	6·9* (−5·4 to 19·3)

* $P<0·05$.

Results are expressed as means with 95% confidence interval in parenthesis.

Table 4. Collagenolytic activity (expressed as DNP-peptide hydrolytic activity) in cervical and uterine tissues from non-pregnant women (group A), term pregnant women (group B) and women in labour (group C)

Tissue specimen	DNP-peptide hydrolytic activity (units/100 mg) Group A (*n* =7)	 Group B (*n* =7)	 Group C (*n* =7)
Fundus uteri	33 (7 to 59)	45 (−13 to 103)	146* (59 to 234)
Isthmus uteri	24 (20 to 28)	111* (85 to 138)	190* (73 to 308)
Cervix uteri	72 (30 to 114)	253* (195 to 312)	266* (165 to 367)

* $P<0·05$.

Results are expressed as means with 95% confidence interval in parenthesis

Table 5. Water content (difference between wet and dry weight) in cervical and uterine tissues from non-pregnant women (group A), term pregnant women (group B) and women in labour (group C)

Tissue specimen	Water content (%) Group A (*n* =7)	 Group B (*n* =7)	 Group C (*n* =7)
Fundus uteri	81·4 (80·0 to 82·8)	82·3 (80·7 to 84·0)	81·4 (79·7 to 83·0)
Isthmus uteri	82·5 (80·1 to 84·9)	83·4 (81·7 to 85·1)	83·1 (80·1 to 86·1)
Cervix uteri	89·6 (78·0 to 81·1)	82·2 (80·6 to 83·7)	81·5 (79·6 to 83·4)

Results are expressed as means with 95% confidence interval in parenthesis.

osamine was decreased in both the fundus, the isthmus and the cervix. The most pronounced change was found in the cervix. The concentration of hyaluronic acid in the fundus, the isthmus and the cervix was lower in term pregnant than in non-pregnant women (Table 6).

An increase of the hydrolytic activity in fundus uteri against the DNP-peptide did not occur until *labour* was established (Table 4).

Discussion

Previous studies have shown that cervical dilatation during labour is closely related to the concentration and physical state of cervical collagen (Ekman *et al.* 1986).

The present results indicate that not only the cervical connective tissue but also the connective tissue of corpus uteri undergo a ripening process similar to that found in the cervix. The collagen in the fundus seems to differ somewhat from that in the cervix, a substantially larger proportion of collagen was extractable by pepsin digestion in the fundus than in the cervix, which indicates fewer cross-linkages between the collagen fibres in the corpus.

We also found that the decrease in collagen concentration at term pregnancy and during labour was highest in the cervix. Furthermore, the increase in solubility by pepsin digestion was more pronounced in the cervix than in the fundus, suggesting that a more extensive remodulation takes place in the cervical connective tissue at term. These findings emphasize the importance of cervix uteri as a dynamic connective tissue organ in late pregnancy and during labour.

In earlier studies we have characterized and measured one proteoglycan in the cervical connective tissue (Uldbjerg *et al.* 1983*b*). Our current results indicate that more than one proteoglycan may exist in the corpus uteri. Before definite conclusions can be drawn about the remodulation process in the corpus uteri, further investigations are needed to find out the exact organization of the connective tissue of the corpus uteri. In particular, the content and characterization of the uterine proteoglycans must be established. Previous and present findings suggest that the state of the cervical connective tissue reflects that of the corpus uteri.

A difference was noted in the collagenolytic activity in the fundus at term pregnancy and during labour. Thus, we found no increase in this activity despite a large reorganization of the fundus tissue. Further investigations using other

Table 6. Sulphated glycosaminoglycans (S-GAG) and hyaluronic acid (HA) (determined as hexosamine) in cervical and uterine tissue from non-pregnant women (group A), term pregnant women (group B) and women in labour (group C)

	Hexosamine (μg/mg w/w)		
Tissue specimen	Group A (n =7)	Group B (n =7)	Group C (n =7)
HA			
Fundus uteri	0·138 (0·124 to 0·151)	0·09* (0·074 to 0·106)	0·123 (0·107 to 0·139)
Isthmus uteri	0·111 (0·081 to 0·142)	0·085 (0·059 to 0·111)	0·163* (0·133 to 0·194)
Cervix uteri	0·199 (0·156 to 0·241)	0·067* (0·024 to 0·109)	0·115* (0·063 to 0·167)
S-GAG			
Fundus uteri	0·318 (0·268 to 0·368)	0·18* (0·122 to 0·238)	0·163* (0·105 to 0·221)
Isthmus uteri	0·279 (0·249 to 0·309)	0·186* (0·163 to 0·209)	0·21* (0·174 to 0·246)
Cervix uteri	0·346 (0·294 to 0·398)	0·148* (0·096 to 0·200)	0·208* (0·149 to 0·266)

* $P<0{\cdot}05$.

Results are expressed as means with 95% confidence interval in parenthesis.

substrates for proteases and collagenases are needed to elucidate this difference.

The ultimate biological significance of the remodulation of the connective tissue in the human myometrium is only speculative. It might be that a breakdown of the connective tissue within the myometrium may enhance a co-ordinated uterine activity, for instance by facilitating the formation of gap junctions (Scott & Orford 1981; Garfield & Hayashi 1981). If so, this 'priming process' of the myometrium is an important contribution to a subsequent effective labour and delivery.

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Ethnic influence on uterine activity in spontaneous normal labour

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Summary. Uterine activity in spontaneous normal labour was studied in Singaporean Malay women at term with a singleton vertex presentation. Nulliparae had significantly higher uterine activity compared with their multiparous counterparts. Uterine activity in the Malay population was compared with that of a similar Chinese population. When controlled for parity, maternal height and birthweight of babies, there was no difference in uterine activity between the two groups.

In contrast to disease processes, physiological functions in man appear to be uninfluenced by ethnic differences when controlled for environmental factors or physical characteristics of the individual. The rate of progress of labour is similar in different ethnic groups (Duignan *et al.* 1975). Uterine activity in patients with normal progress of labour has been described but not compared in various ethnic groups (Cowan *et al.* 1982; Steer *et al.* 1984; Gibb *et al.* 1984). It is controversial whether parous women have lower cervical-dilatation-specific uterine activity values than nulliparae when controlled for rate of progress of labour, maternal height and infant birthweight (Huey *et al.* 1976; Steer *et al.* 1984; Arulkumaran *et al.* 1984). For uterine activity profiles derived from one ethnic group to be used for clinical management of a different ethnic group it is important that these ethnic groups have been demonstrated to have similar uterine activity.

We have reported uterine activity in Singaporean Chinese patients but not in Singaporean Malay patients. We studied the effect of parity on uterine activity in Malay women and compared the findings with those in a control group of Chinese women. The multiracial composition of the Singaporean population makes it particularly suitable for such a study

Subjects and methods

Women of Malay origin, at least 152 cm tall, with a singleton vertex presentation admitted in spontaneous labour at term to the labour ward in Kandang Kerbau Hospital, Singapore, were recruited for the study In the active phase of labour when the cervix was ≥3 cm dilated the membranes were ruptured and a Gaeltec intrauterine catheter was inserted after calibration with a Sonicaid FM 3R or FM 6 (Sonicaid Ltd, Quarry Lane, Chichester, UK) fetal monitor as instructed in the Sonicaid operating handbook. The fetal heart rate was monitored continuously using a scalp electrode. The patients were nursed in the lateral position in the first stage of labour. No epidural analgesia was used; intramuscular pethidine, 75 mg, or a mixture of 50% oxygen and 50% nitrous oxide was used for pain relief. Vaginal examinations were performed every 2–3 h to assess the progress of labour. The

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Table 1. Maternal and neonatal characteristics of the population studied

	Nulliparae		Multiparae	
	Chinese (n=35)	Malay (n=35)	Chinese (n=35)	Malay (n=35)
Age (years)	24·9 (2·8)	24·1 (3·2)	28·2 (3·9)	27·2 (4·1)
Height (cm)	157·4 (3·5)	156·4 (3·9)	157·5 (4·1)	156·9 (2·6)
Gestational age (weeks)	39·3 (1·1)	39·0 (1·5)	39·4 (1·1)	39·6 (1·4)
Birthweight (g)	3153 (354)	3150 (386)	3282 (396)	3239 (353)

Results are mean (SD) values.

uterine activity was quantified on-line by the Sonicaid uterine activity integrator incorporated in the Sonicaid fetal monitor until the cervix was fully dilated. The active contraction area measurements obtained every 15 min were allocated in a progressive manner to the observed progress in cervical dilatation. Patients with a normal progress of labour with a rate of cervical dilatation of 1 cm/h or within 2 h of a line drawn parallel and to the right of this line were included in the study. Those with slower labours needing augmentation of labour and those who required operative delivery were excluded from the study.

Data on age and height, period of gestation, infant birthweight, Apgar scores at 1 and 5 min and cord artery blood pH values were recorded in a computerized coding sheet before the patient was transferred from the labour ward. Uterine activity values were analysed individually and collectively using a computer program that could selectively analyse all or some of the values to derive centiles for each cervical dilatation. The four readings obtained over 1 h were

Table 2. Cervical-dilatation-specific uterine activity by centiles in Malay nulliparae

Cervical dilatation (cm)	Uterine activity centiles in kPas/15 min					No. of readings
	10th	25th	50th	75th	90th	
3	547	644	980	1492	2350	12
4	613	780	960	1430	1663	31
5	542	773	1113	1480	1745	44
6	640	890	1210	1530	2011	47
7	764	1112	1479	1871	2359	50
8	1101	1369	1670	2170	2407	50
9	1375	1550	1960	2500	2500	61
3–9	746	1000	1450	1940	2404	295

Table 3. Cervical-dilatation-specific uterine activity by centiles in Malay multiparae

Cervical dilatation (cm)	Uterine activity centiles in kPas/15 min					No. of readings
	10th	25th	50th	75th	90th	
3	370	553	686	915	1070	16
4	510	639	825	1110	1265	24
5	498	793	1005	1265	1621	38
6	362	800	1000	1503	2066	41
7	389	875	1249	1543	1973	42
8	610	992	1348	1635	1820	44
9	1087	1366	1603	2169	2500	46
3–9	524	820	1165	1540	1983	251

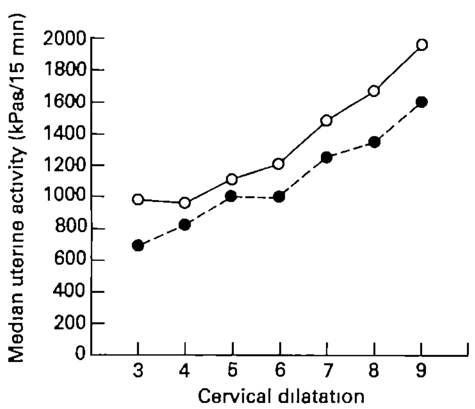

Fig. 1. Comparison of median cervical-dilatation-specific uterine activity in Malay nulliparae (-O-) *vs* multiparae (--●--).

allocated to the cervical dilatation appropriate to the progress of labour in that hour. In some women the second 15-min readings after insertion of the catheter were high compared with the first or third reading and were not included in profile construction. Cervical-dilatation-specific uterine activity values were analysed collectively and profiles constructed for nulliparae and multiparae.

The median uterine activity profile in Malay nulliparae was compared with that in Malay multiparae using the Mann–Whitney *U*-test. The median uterine activity values in the Malays were compared with those in 35 nulliparous and 35 multiparous Chinese women matched for maternal height and birthweight reported by Gibb *et al.* (1984) and Arulkumaran *et al.* (1984) using the Mann–Whitney *U*-test.

Results

The maternal and neonatal characteristics of the population studied are shown in Table 1. There were no statistically significant differences between the Chinese and Malays in mean age, height, period of gestation or birthweight when controlled for parity. Of the 35 Chinese multiparae, 25 had one previous vaginal delivery, eight had two, and two had three or more. Of the 35 Malay multiparae, 27 had one, six had two, and two had three or more vaginal deliveries. There was no difference in the parity distribution between the Chinese and Malays when compared by odds ratios. All the babies had Apgar scores >6 at 1 and 5 min. All the Malay babies had umbilical cord artery blood pH values >7·15. In the Chinese population umbilical vein blood pH values were recorded and all babies had pH values >7·25.

The cervical-dilatation-specific uterine activity profiles of the Malay nulliparae and multiparae are shown in Tables 2 and 3. A wide range of activity was associated with normal progress of labour. The median uterine activity values in the Malay nulliparae and multiparae are illustrated in Fig. 1. The nulliparae had significantly higher uterine activity values than the multiparae except at 5 and 6 cm dilatation.

The cervical-dilatation-specific median uterine activity in the Malay and Chinese population controlled for parity is shown in Table 4. In the nulliparae there was no statistically significant difference in median uterine activity between the two ethnic groups except at 5 and 8 cm. However, there was no difference in the median

Table 4. Cervical-dilatation-specific median uterine activity (kPas/15 min) in Malay and Chinese population controlled for parity

Cervical dilatation (cm)	Nulliparae		Multiparae	
	Chinese (n=35)	Malay (n=35)	Chinese (n=35)	Malay (n=35)
3	1235 (19)	980 (12)	720 (20)	686 (16)
4	1256 (34)	960 (31)	781 (31)	825 (24)
5	1269 (42)	1113 (44)*	979 (38)	1005 (38)
6	1370 (41)	1210 (47)	1058 (34)	1000 (41)
7	1365 (52)	1479 (50)	1148 (42)	1249 (42)
8	1367 (61)	1670 (50)**	1375 (43)	1348 (44)
9	1870 (87)	1960 (61)	1681 (44)	1603 (46)
3–9	1440 (336)	1450 (295)	1140 (252)	1165 (251)

Number of readings for each cm dilatation excluding the second value is given in parenthesis
* $P<0{\cdot}05$; ** $P<0{\cdot}01$.

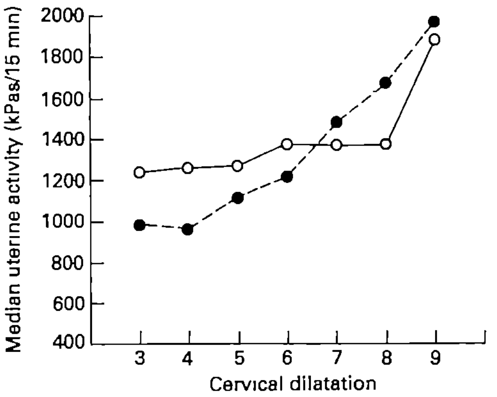

Fig. 2. Comparison of median cervical-dilatation-specific uterine activity in nulliparae Chinese (-○-) *vs* Malay (–●–).

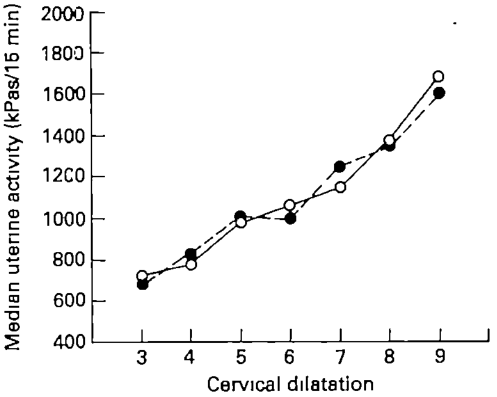

Fig. 3. Comparison of median cervical-dilatation-specific uterine activity in multiparae Chinese (-○-) *vs* Malay (–●–).

uterine activity for the overall labour from 3 to 9 cm (Fig. 2). In multiparae there was no difference in the uterine activity profiles between the Chinese and Malays (Fig. 3).

Discussion

These results support our earlier findings that nulliparae have higher uterine activity values than multiparae (Arulkumaran *et al.* 1984) when controlled for maternal height, period of gestation, presentation, rate of cervical dilatation and infant birthweight. Recent studies by Al-Shawaf *et al.* (1987) and Fairlie *et al.* (1988) on uterine activity in Arabian and Caucasian populations further support this; they found the uterine activity profile in their nulliparae and multiparae to be similar to that reported from our institution in a Chinese population (Gibb *et al.* 1984; Arulkumaran *et al.* 1984). We conclude that the uterine activity profile in our Malay population was similar to that of our Chinese in spontaneous normal labour when controlled for parity, certain maternal characteristics and the rate of progress of labour.

This lends support to the hypothesis that the human uterus acts in a similar way in different races. The presence of uterine pathology such as fibroids, short maternal stature, abnormal pelvic shape, fetal macrosomia and other 'pathological variables' may lead to ethnic differences more apparent than real. It is therefore reasonable to believe that normal profiles may be applied to many racial groups and therefore contribute to management when intrauterine pressure monitoring is used. The role of such monitoring and the units of measurement requires further study.

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Some endocrinological events associated with early pregnancy failure

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Summary. Serial measurements of serum progesterone, oestradiol, human chorionic gonadotrophin (hCG) and human placental lactogen (hPL) have been determined in 33 women experiencing early pregnancy failure and compared with the values of the same hormones in 72 healthy women having uncomplicated pregnancies. Steroid production by the corpus luteum seemed similar in both groups up to 6 weeks gestation but thereafter placental steroidogenesis was not evident in those women in whom spontaneous pregnancy losses occurred. Placental production of the two protein hormones, hCG and hPL, did take place, and whereas the circulating levels were not as high as in normal pregnancies, levels did usually increase before clinical evidence of miscarriage occurred. hCG was not a sensitive discriminator of subsequent failure. In these women there were no significant hormone differences between those with evidence of a fetus and those without.

Attempts to describe the endocrinological events preceding miscarriage are made difficult by the relative imprecision of the definition of miscarriage. In the UK it is applied to any pregnancy ending before 28 weeks gestation in which the fetus does not show signs of life. On such a definition a woman expelling a blighted ovum at 8 weeks gestation is equivalent to a woman losing a well-developed fetus at 26 weeks gestation, yet such patients would not have similar endocrinological findings on clinical presentation. As a less extreme example, do women at 8 weeks gestation with a living fetus have a similar endocrinological status whether they subsequently go on to give birth to a live healthy child at term or lose the pregnancy at 9 weeks?

Studies of pregnant women which begin at the onset of clinical symptoms will not clarify the problem because fetal death may precede expulsion of the products by several days or weeks. We began prospective studies of a large population of women who were willing to offer regular blood samples over the time conception was being attempted and throughout their subsequent pregnancy. Our interests were wide-ranging and we therefore included healthy nulliparae, parous women with uncomplicated past obstetric histories, women with previous miscarriages, and those with a wide spectrum of medical and obstetric disorders. We report our findings concerning the endocrinological changes in 33 women who experienced early pregnancy failure (EPF) and in 72 who had uncomplicated pregnancies ending in the birth of live healthy infants.

Subjects and methods

All the women participating in the study had either not used oral contraceptive agents or had discontinued their use 3 months previously.

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Table 1. Clinical details of the women in the study

	Normal group (n = 72)	Early pregnancy failure group (n = 33)
Age (years) Mean	29	30
(range)	(22–39)	(21–38)
Primigravidae	22	3
Gestation at delivery (weeks)		
6/7	—	2
8/9	—	7
10/11	—	11
12/13	—	7
14/15	—	5
16	—	1
37/38	17	—
39/40	44	—
41/42	11	—
Birthweight (kg)		
Mean	3·45	
(range)	(2·6–4·5)	

Each woman attended the unit between 09.00 and 09.30 hours having fasted for at least 10 h overnight. The woman sat at rest in a warm, quiet room before a blood sample was obtained from an anticubital vein with minimum haemostasis. The women were asked to attend weekly for 3 months and thereafter about day 21 of each subsequent cycle until conception occurred. Several women conceived during the time of weekly attendance and thus serum samples could be analysed from 1–4 weeks gestation, traditionally timed from the first day of the last menstrual period (LMP). The women were divided into two groups according to the outcome of pregnancy.

Normal group

All the 72 women included in this group were in good general health, they had uncomplicated pregnancies and gave birth to live healthy, singleton infants at term (Table 1). Twenty-two were in their first pregnancy and 50 were parous, 20 of the parous women had experienced one or two early pregnancy failures.

Early pregnancy failure group (EPF)

Of the 33 women in this group, three were in their first pregnancy and 30 were parous. Sixteen experienced an EPF for the first time during this study, four had had one previous EPF and 13 had suffered two or more such losses. All were physically healthy though one woman carried a known balanced chromosomal translocation. Apart from this no anatomical or endocrinological cause for the previous miscarriages had been identified in any of the women.

Two women miscarried at 6–7 weeks gestation, the remainder miscarried or had a uterine curettage between 8 and 16 weeks gestation (Table 1). As most of the women were seen early in pregnancy, ultrasound scanning could be undertaken from a very early stage. An ADR 2130 real-time scanner with a linear array and integrated computer-controlled measuring system was used (Godfrey *et al.* 1981). Ultrasound showed that only eight women developed an obvious fetus with a detectable heart beat before miscarriage whereas 25 had a blighted ovum, that is, ultrasound revealed an enlarging gestational sac but no fetal echoes were ever detected.

Radioimmunoassay of hormones

Progesterone was determined using a rabbit antiserum raised against 11 hydroxy-progesterone-succinate and 1,2,6,7-^{3}H progesterone (specific activity 80–110 Ci/mmol). Assay tubes contained 400 ng danazol to displace progesterone from its binding protein. After incubation, antibody-bound progesterone was separated from the free fraction by dextran-coated charcoal. The reference range was 0·00008–0·004 nmol and the limit of sensitivity was 1·6 nmol/l. The within-assay coefficient of variation (CV) was 5·2% and the between-assay CV was 7·0% (n = 10).

Oestradiol was determined using an antiserum to 17-β oestradiol-6-bovine serum albumin and 2,4,6,7-^{3}H oestradiol (specific activity 80–100 Ci/mmol). The reference range was 0·018–0·92 pmol, and serum samples were assayed after extraction with diethyl ether. Separation was effected by addition of dextran-coated charcoal. The limit of sensitivity was 92 pmol/l. The within-assay CV was 7·5% and the between-assay CV was 7·4% (n = 10).

Human chorionic gonadotrophin (hCG) was measured by a double-antibody radioimmunoassay. The anti-hCG rabbit serum (SB6) and hCG for iodination (CR119) were obtained from the NIAMDD (Baltimore, USA) hormone distribution programme. Iodinated hCG was prepared by the lactoperoxidase method and had a

Table 2. Serum hormone levels in women with successful pregnancies and early pregnancy failure (EPF)

Gestation (weeks)	Subject group	*n*	Progesterone (nmol/l)	Oestradiol (pmol/l)	hCG (units/ml)	hPL (μ-units/ml)
3	Normal	38	33·1 (3·2–333·9)	470 (169–1307)	—	—
	EPF	14	42·0 (15·3–115·8)	422 (158–1119)	—	—
4	Normal	27	66·8 (12·4–356·2)	628 (187–2085)	0·22 (0·002–31·0)	0·003 (0·001–0·014)
	EPF	13	69·6 (40·1–121·2)	613 (228–1652)	0·23 (0·003–18·9)	0·003 (0·001–0·007)
6	Normal	44	74·4 (31·5–177·1)	1325 (492–3586)	13·0 (1·0–168)	0·005 (0·001–0·029)
	EPF	22	59·1 (24·5–143·1)	760** (165–3450)	5·8 (0·7–51·3)	0·004 (0·001–0·012)
8	Normal	63	76·0 (36·9–157·4)	2863 (918–9347)	72·4 (17·0–309)	0·041 (0·005–0·369)
	EPF	29	40·7*** (8·3–196·2)	844*** (143–4962)	15·4*** (0·55–430)	0·010*** (0·001–0·068)
10	Normal	62	85·9 (41·0–180·6)	4760 (1527–14 849)	102·1 (43·4–240)	0·206 (0·051–0·839)
	EPF	16	33·1*** (10·2–108·4)	895*** (235–3387)	23·1*** (4·4–122)	0·034*** (0·005–0·226)
12	Normal	68	93·5 (44·2–198·4)	6679 (1982–22 526)	65·0 (24·0–176)	0·466 (0·141–1·61)
	EPF	10	27·7** (6·4–122·1)	745*** (106–5244)	10·9** (0·9–136)	0·095*** (0·015–0·597)

Normal *vs* EPF (two-sample *t*-test): $^{**}P<0{\cdot}01$; $^{***}P<0{\cdot}001$.
Results are geometric means with ranges (±2 SD) in parentheses.

specific activity of 60–90 μCi/μg. The standard used was the International Reference Preparation (IRP) of hCG for immunoassay (73/357). Male serum was added to standards and diluted samples in the assay to counteract any non-specific serum effects. The within-assay and between-assay CV were 1·9% and 3·6% respectively ($n = 10$). The reference range was 5 to 120 iu/l. The cross-reaction with LH was 10·4% expressed on a molar basis.

Human placental lactogen (hPL) was measured by a double-antibody immunoassay using the first IRP of hPL (73/545) as standard. The same preparation was used for iodination by the lactoperoxidase method and had a specific activity of 60–100 μCi/μg. The antiserum was raised in sheep. Male serum was added to standards and the reference range was 0·002–15 μ-units/ml. The within-assay and between-assay CV were 8·7% and 12·5% respectively ($n = 15$).

Statistical analyses

Two-sample *t*-tests and paired *t*-tests on log-transformed data were employed. The reference range for normal values was constructed as the geometric mean ±2 SD. Comparisons of data trends across occasions between the two groups were made using the Mann–Whitney *U*-test.

Results

The changes in serum concentration of the four major pregnancy hormones, progesterone, oestradiol, hCG and hPL, are detailed.

Normal group

Aspillaga *et al.* (1983*a*) reported the endocrinological changes in a group of 32 normal healthy women studied throughout pregnancy. We have now studied 72 women and our findings are similar. The hormonal changes in early pregnancy are detailed in Tables 2 and 4 and compared with the findings in the EPF group.

Table 3. Serum hormone levels in early pregnancy in women with early pregnancy failure (EPF) by presence of fetal echoes

Gestation (weeks)	Subject group*	*n*	Progesterone (nmol/l)	Oestradiol (pmol/l)	hCG (units/ml)	hPL (μ-units/ml)
6	wFe	16	64·6 (27·3–151·1)	793 (158–4033)	5·1 (0·6–46·2)	0·003 (0·001–0·012)
	Fe	6	46·7 (19·7–110·7)	672 (191–2382)	9·0 (1·3–62·5)	0·004 (0·001–0·014)
8	wFe	22	39·4 (7·0–224·5)	818 (121–5465)	13·5 (0·3–548)	0·008 (0·001–0·054)
	Fe	7	43·9 (16·2–119·3)	918 (217–3861)	22·9 (4·4–121)	0·016 (0·002–0·105)

*wFe, Without fetal echoes; Fe, with fetal echoes.

Results are geometric means with ranges (±2 SD) in parentheses. There were no significant differences between the Fe and wFe groups (two-sample *t*-test).

EPF group

The mean serum concentrations of the four hormones are shown in Table 2. Eight patients developed an obvious fetus with a detectable heartbeat and 25 had a blighted ovum, but as there were no statistically significant differences between the two groups for any of the hormones (Table 3) the results have been combined in a single group. The differences in hormone concentrations which occurred between occasions in each patient were calculated and the mean values for the differences at each stage of pregnancy are given in Table 4. This helps to diminish the problem of multiple significance testing, but as the number of women remaining in the EPF group becomes smaller with advancing gestation, trends in the hormone changes must be treated with caution. The changing hormone levels in eight women in the EPF group, for whom there were five or more observations available, are shown in Figs 1–4 against the normal range expressed as ± 2 SD from the normal mean.

Progesterone

There was a similar increase in the serum concentration of progesterone in both the normal and EPF groups until 6 weeks gestation, but an

Table 4. Trends in serum hormone levels in early pregnancy

Gestation (weeks)	Subject group	*n*	Progesterone (nmol/l)	Oestradiol (pmol/l)	hCG (units/ml)	hPL (μ-units/ml)
3–6	Normal	28	25·8**	767***	19·5***	0·004***
	EPF	12	19·0*	444**	8·7**	0·001*
	N *vs* EPF		NS	*	*	NS
6–8	Normal	40	−0·5	2209***	76·0***	0·065***
	EPF	19	−22·3***	73	18·1***	0·011***
	N *vs* EPF		***	***	***	***
8–10	Normal	57	9·7***	1930***	15·9*	0·193***
	EPF	16	−15·4*	−547*	−8·4	0·036**
	N *vs* EPF		***	***	NS	***
10–12	Normal	60	9·4***	2642***	−38·0***	0·286***
	EPF	7	−25·2	−701	−34·0**	0·060
	N *vs* EPF		***	***	NS	***

The difference in hormone concentration across occasions was calculated for each patient and the mean shown above was tested for significance (paired *t*-test)

The trends of the two subject groups were compared with respect to differences across occasions (N *vs* EPF) and tested for significance (Mann–Whitney *U*-test).

NS, Not significant, *$P<0{\cdot}05$; **$P<0{\cdot}01$; ***$P<0{\cdot}001$.

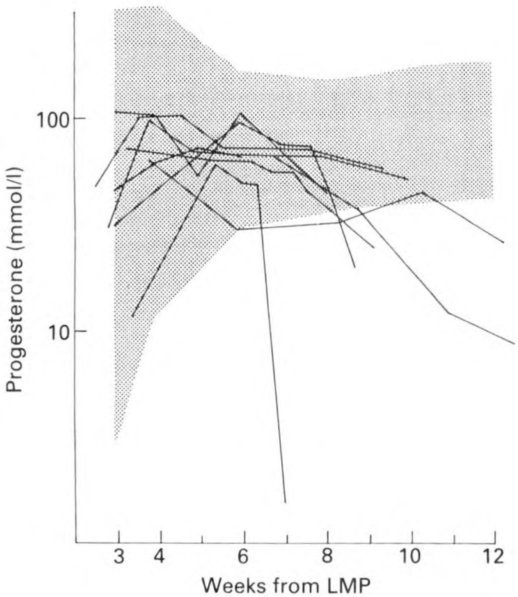

Fig. 1. Serum progesterone values in eight women with early pregnancy failure plotted against the normal range expressed as ±2 SD from the mean. LMP, Last menstrual period.

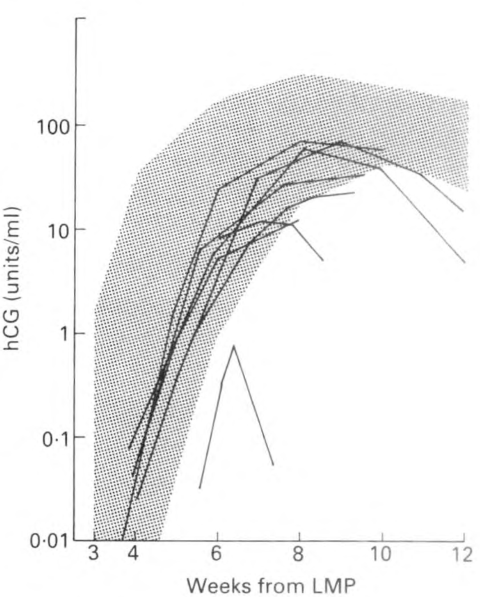

Fig. 3. Serum human chorionic gonadotrophin (hCG) values in eight women with early pregnancy failure plotted against the normal range expressed as ±2 SD from the mean.

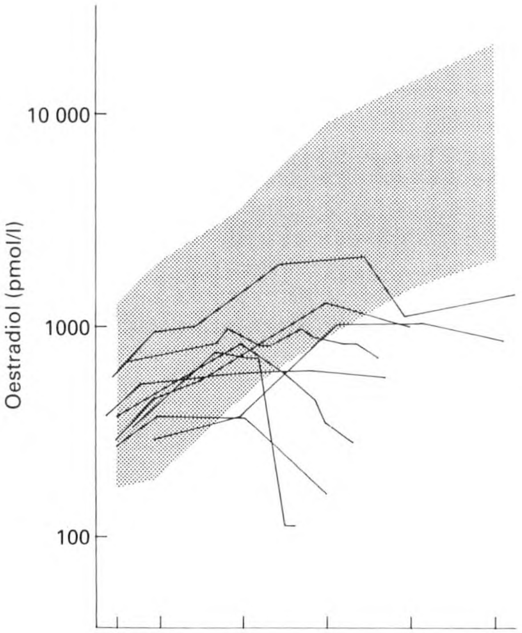

Fig. 2. Serum oestradiol values in eight women with early pregnancy failure plotted against the normal range expressed as ±2 SD from the mean.

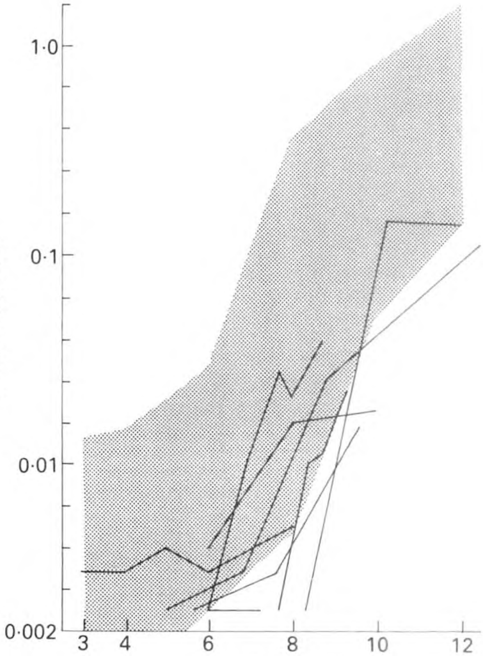

Fig. 4. Serum human placental lactogen (hPL) values in eight women with early pregnancy failure plotted against the normal range expressed as ±2 SD from the mean.

apparent failure to maintain levels thereafter in the EPF group. By 8 weeks gestation the mean concentration in the EPF group was significantly lower than in the normal group ($P<0{\cdot}001$) and this decline continued until 12 weeks. Individual women within the group demonstrated a similar pattern of response, although the onset of the marked decrease in progesterone values was a function of the time that clinical symptoms occurred. Figure 1 shows the progesterone values in the eight women in the EPF group who had five or more observations, they were representative of the group as a whole.

Oestradiol

Because of the progressive increase in the circulating levels of this hormone during normal pregnancy the changes in the EPF group were easier to determine. Although there was a significant increase ($P<0{\cdot}01$) in the serum oestradiol concentrations in the EPF group between 3 and 6 weeks gestation, this was less than in the normal group ($P<0{\cdot}05$). Thereafter the mean values remained static until about 10 weeks then decreased. Figure 2 shows that most of the eight women illustrated had oestradiol values outside the lower limits of the normal range before 10 weeks gestation.

hCG

The placental protein hormones behaved differently. The mean values for hCG plotted against the response of normal women were similar though lower at each stage of gestation. The remarkable attempt of the placenta to produce hCG, even in the absence of a fetus, is well demonstrated by the eight women illustrated in Fig. 3. Sufficient data were available between 4 and 6 weeks to calculate the doubling time for hCG in 12 women in the EPF group, and the mean time (2·1 days, SD 0·56) was not significantly different from the doubling time in 19 women in the normal group (mean 2·1, SD 0·67 days) for whom observations were available in this period. Thereafter, however, the rate of increase in circulating hCG levels slowed in the EPF group to a significant extent ($P<0{\cdot}001$) and the mean values at 8 weeks and beyond were all significantly lower than in the normal group. For 13 (45%) of the 29 women reaching 8 weeks gestation the hCG concentrations were >2 SD below the normal mean and declined thereafter to below the normal range in the majority; interestingly the rate of decrease paralleled the physiological decrease occurring in normal women at this stage, paired analysis showing no difference.

hPL

This placental protein hormone also tried hard to conform to the normal pattern. Concentrations continued to increase though the mean concentration achieved at 8 weeks and after was significantly lower ($P<0{\cdot}001$) than that in the normal group. By 8 weeks about half the women had concentrations below the normal range although concentrations were still increasing.

Discussion

One difficulty in assessing the relation between endocrinological changes and early pregnancy failure is deciding when hormonal influences may play a part. Is there, for example, a condition of 'corpus luteum deficiency'? In such instances it has been suggested that progesterone production by the corpus luteum is insufficient to support pregnancy during the phase before the placenta undertakes significant steroidogenesis. Surgical removal of the whole corpus luteum before about day 56 of pregnancy will usually cause miscarriage, but this can be prevented by giving parenteral progesterone though not oestradiol (Csapo & Pulkkinen 1978). Thus some progesterone is necessary for the maintenance of early pregnancy but whether there is a specific minimum concentration to ensure success is uncertain. In our study the women who miscarried had circulating progesterone concentrations which were not significantly different from those in the normal group during the first 4–6 weeks. The decline thereafter seemed to reflect a failure of the placenta to contribute to steroid production rather than any intrinsic failure on the part of the corpus luteum.

This 'placental failure' is supported by the oestradiol findings; the EPF group had significantly lower plasma oestradiol levels than the normal group from 6 weeks onwards, a finding reported from three other longitudinal studies in small groups of women (Jovanovic *et al.* 1978; Schweditsch *et al.* 1979; Ho Yuen *et al.* 1981).

Finally 17-hydroxy progesterone concentrations before 6 weeks gestation in women who subsequently miscarry have been reported to be within the normal range (Aspillaga *et al.* 1983*b*); as the hormone comes from the corpus luteum and not the placenta the implication appears to be that many women who experience EPF have perfectly adequate corpora lutea. Furthermore, the levels of relaxin (predominantly a corpus luteum product) have been reported to be normal when hCG values were subnormal in impending EPF (Quagliarello *et al.* 1981). Subsequently abnormal 17-OH-progesterone and relaxin levels may reflect inadequate luteal stimulation by the failing placenta.

While it appears that in pregnancies which fail subsequently, placental steroid production is reduced or absent between 6 and 8 weeks, the ability to manufacture hPL and hCG is still present, though muted. Our data suggest that circulating levels of these placental protein hormones do increase during the first 8–10 weeks in women progressing this far but the values are consistently lower than those in women who have successful pregnancies. This is in keeping with the report of Biswas *et al.* (1980) who noted that hPL values were often normal in women before clinical signs of impending miscarriage appeared.

More has been published about hCG levels in women with EPF, including several longitudinal studies. In general terms, concentrations up to 6 weeks are normal, but remain static or decrease thereafter (Braunstein *et al.* 1978; Mellows *et al.* 1980; Dhont *et al.* 1982). Such values must be influenced by the stage of pregnancy at which individual pregnancies have 'failed', the time the blood samples were obtained and the reliability of the menstrual dates. To get around some of these difficulties it has been suggested that serial measurements which allow the rate of increase (or doubling time) of circulating hCG to be determined could be useful. Batzer *et al.* (1981, 1983) and Pittaway *et al.* (1985) reported that the rate at which hCG increased could identify women who miscarried subsequently, with a sensitivity of 60–80%, but this was not our experience. Furthermore, Yovich *et al.* (1986) reported 18 anembryonic pregnancies in infertility patients in whom hCG was significantly lower by 4 weeks gestation, but oestradiol and progesterone did not differentiate from normal until 7 weeks; these findings are in direct contrast to our data.

More recently, hCG levels have been said to predict the outcome of pregnancies following in-vitro fertilization (Deutinger *et al.* 1986; Confino *et al.* 1986), but other evidence questions the sensitivity of the test (Tarlatzis *et al.* 1986; Okamoto *et al.* 1987; Cole *et al.* 1987). In a series of 18 women with unsuccessful outcome of embryo transfer, Cole *et al.* (1987) reported that only one had detectable free β-subunit of hCG by 28 days after transfer whereas of 30 women who went successfully to term 28 had detectable circulating levels of the β-subunit at this stage. The reasons for this are not clear but may indicate some independent secretion of the β-subunit during successful early proliferation and differentiation of the trophoblast; the subunit may not necessarily be coming from previously formed whole hCG.

A knowledge of circulating levels of progesterone, oestradiol, hCG and hPL in women with clinical evidence of threatened miscarriage is not particularly helpful. If ultrasound scanning does not detect fetal heart action, the levels of these hormones will be low (Westergaard *et al.* 1985) and no single hormone will predict the subsequent outcome with more efficiency than the others (Salem *et al.* 1984). In such instances there is little to suggest that these low hormone concentrations were causal of the clinical condition rather than a consequence. If, on the other hand, ultrasound reveals fetal heart action at the time of clinical presentation many of the women who subsequently miscarry will have values for the four hormones which are within the normal range until miscarriage or fetal death (Jouppila *et al.* 1980; Westergaard *et al.* 1985).

Because of the lack of firm evidence from prospective controlled trials that any type of hormonal 'deficiency' is the cause of miscarriage, the value of giving progesterone (Willcox *et al.* 1985) or hCG (Harrison 1985) remains to be proven even in women shown by sonar scanning to have a living fetus. Furthermore there is no clear evidence of any early endocrinological differences between women with a fetus and those without. We found no significant hormone differences at 6 or 8 weeks after the last menstrual period between these groups, suggesting that failure of development of the embryo has no immediate effect on hormone synthesis by trophoblastic tissue. In our experience, most women with early pregnancy failure never develop a fetus (i.e. have a blighted ovum), and hormonal prophylaxis in such instances would be a waste of time (Lind & MacFadyne 1986).

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Direct chromosome analysis in the second and third trimesters by placental biopsy in 30 pregnancies

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Summary. Direct chromosome analysis was performed on placental villi obtained by ultrasound-guided transabdominal needle aspiration in 30 women at between 23 and 37 weeks gestation. Placental biopsy is simple in the presence of severe oligohydramnios where fetal blood sampling is usually more difficult. Direct karyotyping of placental villi is more rapid than chromosomal analysis from fetal blood and from amniotic fluid. Two chromosomal anomalies were discovered: one trisomy 18 and one 6p+. Villus sampling failed in one woman and two samples obtained at 36 and 37 weeks gestation could not be karyotyped. The procedure did not affect the outcome of the pregnancy.

Formerly, chorionic villus sampling for fetal karyotyping was restricted to the first trimester of pregnancy, but now it can be used later in pregnancy when a fetal abnormality is suspected in a routine ultrasound examination (Nicolaides *et al.* 1986; Szabo *et al.* 1986; Cook & Young 1986; Lilford *et al.* 1987; Basaran *et al.* 1988; Eiben *et al.* 1988; Saura *et al.* 1988*b*). In the presence of oligohydramnios, amniocentesis and fetal blood sampling are sometimes not possible. In these cases, placental tissue sampling allows rapid chromosomal karyotyping of the fetus, using the 'direct method'. Because the method is so simple, we have been able to extend the use of fetal karyotyping in all pregnancies with suspected fetal abnormality on ultrasound. This report is based on 30 pregnancies investigated in this way.

Subjects and methods

Placental tissue was sampled in 30 pregnant women. Their mean age was 28 years (range 20–38), and gestational age was between 23 and 37 weeks. The placenta was located by ultrasound (Kreitz Sectorial time probe of 3·5 MHz). Under local anaesthesia, a 16-gauge needle (initially we used a 12–14-gauge needle) was introduced through the abdominal wall under ultrasound guidance, into the placenta, equidistant from the basal and chorionic plates. Placental villi were collected by continuous suction using a 20-ml syringe, combined with a rotating and a gentle up and down movement of the needle, which had been rinsed with heparin. All samples were visually estimated to be about 5 mg in comparison with a reference specimen. Using aseptic techniques, the samples were placed into

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tubes containing 10 ml of culture medium (RPMI flow), preheated to 37°C and supplemented with 15% fetal calf serum (seromed, 5% ultroser (IBF)). After inspection under the binocular microscope, the sample was washed several times with the same medium.

Cytogenetic analysis

A direct method of analysis (Simoni *et al.* 1983) was modified (Saura *et al.* 1988*a*) to obtain the chromosomal preparations. The placental villi were divided into portions of 1–2 mg and placed in 30-mm petri dishes containing 5 ml of culture medium supplemented with 0·05 ml of 10 μg/ml colcemid (GIBCO) and incubated for 1 h. The medium was aspirated and 5 ml of 1% sodium citrate was added for 10 min. This solution was then discarded and fresh fixative (3 parts methanol to 1 part glacial acetic acid) was added and left for at least 10 min at room temperature; this was repeated three times.

The sample was poured on to filter paper and immersed in two drops of 50% diluted acetic acid. The villi were teased with the tip of a needle for 5 min to facilitate cell dissociation. This step was controlled under the inverted microscope. Once the cells has been loosened, 8 drops of methanol (4 parts methanol to 1 part 50% acetic acid) were added. One drop of this suspension was placed on a slide on a hot plate at 65°C and this resulted in spontaneous spreading. Ten slides were prepared and stained with 4% Giemsa, 24 h later R-banding (Dutrillaux & LeJeune 1971) or G-banding (Seabright 1971), or both, were carried out and at least 15 metaphases were counted and analysed.

Results

Between May 1987 and June 1988 30 pregnancies were investigated in the second or third trimester with placentocentesis for karyotyping. The characteristics of the 30 pregnancies are summarized in Table 1. Isolated or non-isolated oligohydramnios was our first indication (Saura *et al.* 1988*b*). Because rapid chromosomal analysis by the direct method is so simple, we have tended to use the technique whenever ultrasound findings gave cause for concern. Whenever possible we used both amniocentesis and placentocentesis. Two chromosomal abnormalities were detected. In one pregnancy, complicated by fetal growth retardation at the 5th centile, club foot and mild polyhydramnios, placental biopsy at 26 weeks identified a trisomy 18, which was confirmed after abortion. In the second pregnancy, ultrasound had revealed a bilateral ureter dilatation, and fetal karyotyping revealed an unbalanced homogeneous chromosome pattern, 46, XY, 6p+ (30 cells).

This result was confirmed before termination by karyotyping of fetal lymphocytes from umbilical cord sampling and by a second placentocentesis. Parental karyotyping was normal. The aborted fetus showed various malformations. Sampling failed in one woman (no villi were obtained after three attempts) and chromosomal analysis failed in two samples which were obtained at 36 and 37 weeks gestation. In these two samples fewer than five metaphases were analysed and this was not sufficient to establish a diagnosis. One fetoplacental discrepancy occurred in one pregnancy where ultrasound had revealed a bilateral ureter dilatation. The placental karyotype was 46, XX and the newborn was a male. The karyotype of blood lymphocytes indicated a homogeneous chromosomal complement of 46, XY on 100 cells. We re-examined our slides from the chorionic villi sampling and confirmed the 46, XX complement on 50 cells (Saura *et al.* 1988*c*). The procedure did not ultimately affect the outcome of the pregnancy.

Discussion

Recent progress in obstetric ultrasound permits detection of 'intrauterine growth retardation', oligohydramnios, polyhydramnios and fetal malformations. When there is no obvious aetiology for the observed signs, it is necessary to consider a chromosomal abnormality. When there is a severe chromosomal abnormality, patient counselling will depend on the diagnosis and the gestational age. The finding may lead to termination of pregnancy, or in some circumstances vaginal delivery, rather than caesarean section, thereby protecting the obstetric future of the woman.

Placentocentesis can represent a good alternative to the usual sampling technique for karyotyping. Amniocentesis becomes difficult in the presence of oligohydramnios, and a delay of 3–4 weeks is usual before results can be obtained. Fetal blood sampling from umbilical cord vessels can be very useful (Daffos *et al.*

Table 1. Indication for and results obtained in 30 pregnancies investigated with placentocentesis

Patient	Maternal age (years)	Gestational age (weeks)	Indication	No of slides scanned	Karyotype	Fetal outcome	Diagnostic confirmation
1	24	27	IUGR, oligohydramnios	4	46 XY	1000 g, bilateral renal agenesis, died at 24 h	ND
2	35	24	IUGR, oligohydramnios	10	46 XY	1450 g, alive and well	ND
3	23	27	IUGR	8	46 XX	2660 g, alive and well	ND
4	27	25	Bilateral ureter dilatation	2	46 XX	3050 g, male 46 XY, bilateral ureter dilatation	Fetoplacental discrepancy at birth
5	27	25	IUGR, oligohydramnios	3	46 XY	Intrauterine death at 28 weeks, similar to previous pregnancy	46 XY confirmed
6	26	34	IUGR, polyhydramnios	10	46 XY	2300 g, multiple deformities, died at 6 days	46 XY confirmed
7	30	30	IUGR, polyhydramnios	4	46 XY	2700 g, hypotonic, died at 48 h	ND
8	34	35	Fetal abnormalities	2	46 XX	3300 g, ovarian cyst	ND
9	28	35	IUGR, oligohydramnios	5	46 XY	1900 g	46 XY confirmed
10	27	31	Heart abnormality	9	46 XY	Induction at 34 weeks, multiple deformities, died at 48 h	46 XY confirmed
11	28	28	IUGR	5	46 XX	3400 g, alive and well	ND
12	24	25	IUGR, oligohydramnios	10	46 XY	Alive and well	ND
13	36	25	Fetal abnormalities, laparoschisis	Failed sampling			
14	20	24	IUGR, polyhydramnios	8	46 XX	2800 g, alive and well	ND
15	30	32	Polyhydramnios	10	46 XY	Neurological disorder	46 XY confirmed
16	26	24	Polyhydramnios, fetal abnormalities	1	46 XX	Intrauterine death at 24 weeks, multiple deformities	46 XX confirmed
17	24	35	Fetal abnormalities	1	46 XY	Induction at 28 weeks, prune belly syndrome	ND
18	24	35	Bilateral ureter dilatation	4	46 XY	3320 g, bilateral ureter dilatation	ND
19	30	27	IUGR, polyhydramnios, fetal abnormalities	2	47 XX, +18	Induction at 28 weeks, multiple abnormalities	47 XX, +18 confirmed
20	22	36	Polyhydramnios	Failed karyotype		3220 g, hypotonic at birth, alive and well	ND
21	20	37	IUGR	Failed karyotype		1700 g, alive and well	ND
22	35	23	Club foot	3	46 XY	3100 g, club foot	ND
23	24	29	IUGR	10	46 XY	3180 g, alive and well	ND
24	21	24	Wide ureters	4	46 XY, 6p+	Induced abortion, multiple deformities	46 XY, 6p+ confirmed
25	27	28	IUGR	2	46 XX	970 g, died at 4 days	ND
26	34	24	Heart malformation	3	46 XY	Induced abortion, severe heart malformation	ND
27	27	33	IUGR	1	46 XY	1350 g, alive and well	ND
28	31	26	IUGR	1	46 XX	3220 g, alive and well	ND
29	25	27	IUGR	9	46 XX	2860 g, alive and well	ND
30	35	22	IUGR, oligohydramnios	2	46 XX	Multiple deformities	46 XX confirmed

IUGR, Intrauterine growth retardation; ND, not done

1983), but sampling can be difficult or impossible when there is oligohydramnios.

On the contrary, placentocentesis is a simple method (Nicolaïdes *et al.* 1986) deriving from that described by Smidt-Jensen & Hahnemann (1984) for chorionic villus sampling during the first trimester. It can be performed at any stage of pregnancy (Lilford *et al.* 1987). The risk of fetal infection seems lower by the transabdominal route (Lilford *et al.* 1987) than by the transcervical route (Szabo *et al.* 1986). The volume of placental villi obtained is sufficient for karyotyping. In our experience the quantity of placental villi obtained was always <5 mg, as such a small amount of material is adequate for chromosomal analysis (Saura *et al.* 1989). The mitotic index on chorionic villi decreases with increasing gestational age; in our hands 35 weeks gestation seems to be a limit, although Nicolaïdes *et al.* (1986) reported a result at 37 weeks.

Our fetoplacental anomaly concerning sex chromosomes can be added to the false-negative finding reported by Eiben *et al.* (1988). These two discrepancies must still lead us to be cautious, although they do seem to represent the principal limiting factor. Further assessment is still necessary, however, in order to ensure that the method is entirely safe and reliable.

It is a simple reproducible method which could be used in all prenatal diagnosis units. Indications could be extended to women over 37 years of age and placentocentesis could provide an alternative to amniocentesis. This new method, applicable after 12 weeks gestation, could provide a more flexible method of prenatal diagnosis of chromosome abnormalities for high-risk couples.

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Epidemiology and trends in hospital discharges for pelvic inflammatory disease in England, 1975 to 1985

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Summary. Hospital Inpatient Enquiry data were analysed to determine trends in hospital discharges for pelvic inflammatory disease in England from 1975 to 1985. Cases where the disease was thought to be related to another condition, e.g. appendicitis, were excluded from the analysis. Discharge rates for both acute and chronic disease increased over the review period and there was a 28% increase in the discharge rate for total disease. Women in their 20s were most likely to be involved and this group showed the greatest increase in the discharge rate, both for acute and chronic disease. In the 20–24-year age group the rate of discharge for acute disease rose by 50%, from 125.6/100 000 in 1975 to 189·0/100 000 in 1985. Patients with a diagnosis of chronic pelvic inflammatory disease tended to be older than those with acute disease. Women who were divorced were more at risk of both acute and chronic forms of the disease than single or married women. Increase in the use of surgery to confirm the diagnosis occurred only for those with chronic disease. About a quarter of patients with acute disease had the diagnosis confirmed surgically, and this proportion did not change in the period studied, although laparoscopy increased as laparotomy decreased.

Pelvic inflammatory disease has important long-term adverse consequences for women of reproductive age. It is difficult to estimate the true incidence of the disease, not only because clinical diagnosis is unreliable—at laparoscopy the diagnosis will be confirmed in only two-thirds of suspected cases (Jacobson & Westrom 1969)—but also because serious infection may occur with few symptoms. However, hospital discharge data can give some indication of trends in diagnosis and are the best available indicator of changes in incidence over time. Hospital discharges for pelvic inflammatory disease increased in England and Wales between 1966 and 1976 (Robinson *et al.* 1981). This paper describes the trends in hospital discharges from 1975 to 1985 and examines certain aspects of the epidemiology of the condition.

Subjects and methods

The Hospital Inpatient Enquiry (HIPE) is based on a 10% sample of deaths in and discharges from national public hospitals. Using these data an estimate of total numbers of discharges for any specified condition can be made. Routinely published information relates only to the principal condition for which patients were treated in hospital. Accordingly, detailed data for this analysis were obtained from the Office of Population Censuses and Surveys. Records were requested for all women discharged with any of the following conditions as a primary or any

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secondary diagnosis: salpingitis and pelvic inflammatory disease; hydrosalpinx; parametritis, pelvic cellulitis and peritonitis; and inflammatory disease of the uterus except cervix.

These conditions can be coded as either acute, chronic or unspecified. Where possible, cases were categorized as acute or chronic on the basis of the original International Classification of Disease (ICD) coding (WHO 1967, 1978). The ICD codes used for acute disease were: ICD 8 Code 612; ICD 9 Codes 0981, 6140, 6143, 6150. For chronic disease the codes were: ICD 8 Codes 0981, 613; ICD 9 Codes 0983, 6141, 6147, 6151. Most cases were originally coded as unspecified. This was true both in the years in which the 8th revision of the ICD was in use—when 86·5% of cases were unspecified—and in the years in which the 9th revision was in use, when 71·7% were coded as unspecified. These cases—ICD 8 Codes 614, 6151, 6160, 6220; ICD 9 Codes 6142, 6144, 6145, 6148, 6149, 6159—were allocated, following the method used by Robinson *et al.* (1981), to the acute category if the patient was admitted on an emergency basis and to the chronic category if the admission was booked. All categories were combined to determine total pelvic inflammatory disease. The records were obtained for the years 1975, 1977, 1979, 1981, 1983 and 1985. ICD 8 was used for coding 1975 and 1977 and ICD 9 for coding the remaining years.

From 1982 the data collected by OPCS refer to patients treated in regional health authorities in England only. Therefore, to maintain consistency all data from Wales have been excluded from this analysis. Cases were also excluded from the analysis if it seemed likely that the episode of pelvic inflammatory disease was related to an accompanying condition or preceding event. On this basis approximately 4·5% of cases each year were excluded because of an accompanying diagnosis such as appendicitis, abdominal malignancy, abortion or childbirth.

Cases were regarded as surgically confirmed if laparoscopy, laparotomy, or any other abdominal operation (e.g. prophylactic appendicectomy) was coded. Patients who either had no operation or had an operation which would not permit inspection of the pelvic organs were regarded as having a clinical diagnosis only. The only exception was if the diagnosis was inflammatory disease of the uterus. Patients with this diagnosis were assigned to the surgically confirmed category if dilatation and curettage was coded.

The 1981 female population of England was used as the standard population and for calculation of rates by marital status.

Table 1. Estimated total numbers of cases and age-standardized rates of hospital discharge for pelvic inflammatory disease/100 000 women aged 15–44, England, 1975–1985

Year	Estimated total number of cases	Age-standardized rates: As a primary condition	Total
1975	11 239	105·6	124·6
1977	11 290	102·2	123·2
1979	11 910	104·3	127·0
1981	13 160	110·3	134·5
1983	15 130	125·4	152·1
1985	16 210	131·8	159·3

Results

Table 1 shows the age-standardized rates per 100 000 for women aged 15–44 years discharged from hospital with a diagnosis of pelvic inflammatory disease. About 17% of patients had the disease coded as a secondary condition. There was a 28% increase in total disease discharge rates between 1975 and 1985. Age-standardized discharge rates were also calculated for both acute and chronic pelvic inflammatory disease. Approximately 65% of disease was acute. Discharge rates for acute disease fell slightly between 1975 and 1979 from 84·6/100 000 to 79·2/100 000 but rose again subsequently to 105·8/100 000 in 1985. The rate of discharge for chronic disease rose steadily from 40·0/100 000 in 1975 to 53·5/100 000 in 1985.

Examination of the age-specific discharge rates for total pelvic inflammatory disease shows that rates of hospital discharge were highest in the 20–24-year age group followed by those in the 25–29-year age group. This is also true for acute pelvic inflammatory disease but not for chronic disease (Table 2). Over the years there was an increase in the rate of discharge for acute disease in women under the age of 35. The most dramatic increase in acute disease was in the 20-24-year age group where, between 1975 and 1985, the rate rose by 50%.

Rates of chronic disease rose in all age groups with the exception of 15–19-year-olds (Table 2).

Table 2. Age-specific discharge rates per 100 000 for acute and chronic disease

Age group (years)	Year 1975	1977	1979	1981	1983	1985
(a) Acute disease						
15–19	111·9	88·6	86·6	95·7	110·0	113·0
20–24	125·6	142·5	132·2	136·1	154·5	189·0
25–29	108·3	95·2	97·0	115·7	130·8	136·7
30–34	65·0	68·3	73·1	67·6	87·5	98·5
35–39	49·5	39·4	45·6	39·5	56·9	44·8
40–44	28·3	33·6	22·9	27·4	35·8	26·7
(b) Chronic disease						
15–19	21·8	15·6	24·3	17·9	19·0	17·0
20–24	37·9	54·1	55·3	52·6	55·5	57·3
25–29	53·5	54·0	64·0	72·1	73·5	75·7
30–34	62·0	55·2	59·0	67·6	68·1	70·4
35–39	43·9	47·8	53·6	63·7	58·1	59·7
40–44	19·2	28·9	30·5	35·7	47·7	45·0

Rates were highest in the 25–29-year age group, and over the study period there was a steady increase in the rates for this age group. In women >35 years of age, discharge rates for chronic disease exceeded the rates for acute disease.

Table 3 shows the extent to which surgery was used in patients with a diagnosis of pelvic inflammatory disease. The percentage of pelvic inflammatory disease which could be regarded as surgically confirmed increased between 1975 and 1985 but this was because of an increasing use of surgery in patients with chronic disease. About one quarter of acute cases underwent surgery which would enable confirmation of the diagnosis and there has been no increase in this proportion since 1975. Over this time period there has been a steady growth in the use of laparoscopy which has tended to replace other forms of surgery. In 1975 only 22·3% of those cases which were surgically confirmed underwent laparoscopy. By 1985, 54·0% of surgically confirmed cases had undergone this procedure. A hysterectomy was performed in about 6% of all cases. Pelvic inflammatory disease was stated as the primary diagnosis in over half these cases and, on average, for the years analysed, 44% of women who underwent hysterectomy were <35 years of age.

The rates of hospital discharge in 1981 for acute and chronic disease by marital status were calculated. Some women described in the official statistics as either single or divorced may well be living in stable relationships with one partner. Unfortunately, the way the data are classified does not permit a clear distinction to be made between those who are cohabiting and those who are not. Women who described themselves as divorced women were most at risk of both the acute and chronic forms of the disease. Discharge rates per 100 000 for total disease were 135·3 for single women, 128·8 for married women and 267·9 for divorced women.

Table 4 lists some of the conditions which accompanied the diagnosis of pelvic inflammatory disease. Gonorrhoea is rarely recorded as an accompanying condition. Infertility, however, is more common, but the percentage of cases with this diagnosis rose only slightly between 1975 and 1985. From 1979 onwards the IUCD (intrauterine contraceptive device) category includes all cases where either the presence or the removal of an IUCD, or complications arising from the use of an IUCD, were coded. Before 1979 only removal of a device was coded. The higher numbers noted in later years probably reflect this change in coding practice.

There was no evidence of any relation between season and hospital discharge rates for either acute or chronic disease. Although most patients were either admitted to or transferred to departments of gynaecology before discharge, a significant proportion (14% on average) were diagnosed and treated in surgical departments. Death in women of reproductive age was a rare outcome—since 1979 the HIPE 10% sample has recorded only one death in women in the 15–44-year age group.

The mean duration of stay decreased each year for both acute and chronic disease. This decrease in duration of stay holds true for all age groups. Average length of stay for total disease fell from 7·6 days in 1975 to 4·1 days in 1985. This decrease in average length of stay has meant

Table 3. Percentage of pelvic inflammatory disease which is surgically confirmed

Year	Percentage surgically confirmed: Acute	Chronic	All disease
1975	25	66	38
1977	26	74	43
1979	22	66	38
1981	24	77	44
1983	22	82	43
1985	26	84	46

Table 4. Conditions accompanying the diagnosis of pelvic inflammatory disease—number of cases in HIPE 10% sample and per cent of total number of cases

	Infertility		Gonorrhoea		Ectopic pregnancy		Presence of IUCD*		Non-specific pain†	
Year	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
1975	35	(3·4)	20	(1·9)	10	(1·0)	8	(0·8)	47	(4·5)
1977	46	(4·1)	10	(0·9)	6	(0·5)	24	(2·1)	62	(5·5)
1979	52	(4·4)	18	(1·5)	7	(0·6)	46	(3·9)	56	(4·7)
1981	68	(5·2)	8	(0·6)	5	(0·4)	39	(3·0)	80	(6·1)
1983	59	(3·9)	19	(1·3)	10	(0·7)	59	(3·9)	88	(5·8)
1985	74	(4·6)	9	(0·6)	6	(0·4)	59	(3·6)	96	(5·9)

The figures show the number of cases in the Hospital Inpatient Enquiry (HIPE) 10% sample and the percentage of total number of cases in parenthesis.

* IUCD, Intrauterine contraceptive device.

† Non-specific abdominal or genitourinary pain.

that, in spite of the increased rate of admission for pelvic inflammatory disease, the total number of hospital bed days used by patients with this condition has fallen by 15% since 1975.

Discussion

There are some important points to be kept in mind when interpreting these data. Firstly, because they are estimates based on a 10% sample they are subject to statistical variation, particularly in categories with small numbers of events. Secondly, hospital discharge data relate to episodes of disease rather than to individual patients. It is therefore not possible to be sure that an increase in hospital discharge rates represents an increase in incidence of disease rather than merely a tendency towards repeated admissions for individual women. Thirdly, during the time period studied there was a revision of the ICD and an alteration in the way in which pelvic inflammatory disease was coded. Under these circumstances it is possible that some of the increase noted may be an artefact consequent on the change in coding. However, discharge rates have continued to increase since 1979 when the 9th revision was introduced in England.

Despite the exclusion of cases where pelvic inflammatory disease was obviously secondary to another condition, some of the cases included will still have developed pelvic infection as a complication of another disease process or following an operative procedure. Nevertheless, it is likely that the rates presented underestimate the risk of hospitalization for pelvic inflammatory disease. There are two main reasons for this. Firstly, data from private hospitals are not included. Secondly, it is widely believed that pelvic inflammatory disease occurs rarely in women who are not sexually active (Westrom 1980). The rates in this paper have been calculated on the basis of all women between the ages of 15 and 44 being equally at risk. The rates for women at risk in the youngest age group are probably much higher than would appear on the basis of the figures presented here, as relatively few of them will be sexually active.

Increases in hospital admission for pelvic inflammatory disease might occur without an accompanying increase in the incidence of the disease if general practitioners changed their threshold for requesting admission so that less severe cases were admitted rather than being treated in the community. The decrease in the average length of stay lends some support to this theory, although average days stay for all conditions has been decreasing (DHSS 1987). Increases in the rate of hospital admission for the disease might also occur in the absence of an increase in incidence if the severity of the disease had changed, so that women with pelvic infection presented a more dramatic clinical picture. However, the non-gonococcal organisms which are now thought to be the cause of most infections produce an illness which is less, rather than more severe, in its initial presentation (Svensson *et al.* 1980).

The difficulties with respect to accurate diagnosis of pelvic inflammatory disease also contribute to uncertainties about trends in incidence. It is possible that the increase in rates noted here is due to diagnostic drift; for example, instead of diagnosing non-specific abdominal pain, doctors may now have a greater tendency to label women with this symptom as suffering from pelvic inflammatory disease. The use of surgery in the diagnosis of the disease is interesting in this respect. There has been no increase in the percentage of acute disease which is surgically confirmed. Although the use of laparoscopy has increased in this group, it has replaced other operative procedures such as laparotomy. The explanation for the increase in acute disease rates is, therefore, not a result of improvement in diagnosis. However the rising rate of chronic disease may well be attributable to improved recognition because of increased use of surgery. It is also possible that an increase in women seeking treatment for infertility has contributed towards the upward trend in diagnosis of chronic disease.

The findings that women in their 20s and divorced women are most at risk are in accordance with the results of previous studies both in this country (Robinson *et al.* 1981) and elsewhere (Jones *et al.* 1980; Westrom 1980; Washington *et al.* 1984). However, rates of hospitalization for pelvic inflammatory disease in the United States and Canada are many times higher than the estimates reported here. In Canada in 1981 the rate for the 20–24-year age group was approaching 440/100 000 (Todd 1986); this figure does not include patients coded as suffering from inflammatory disease of the uterus (ICD 9 Codes 6150, 6151, 6159). Patients with these codes formed 5% of the discharges in this study. In the United States the rate for the 20–24-year age group is even higher, for the period 1975 to 1981 the rate of discharge for the same ICD codes as were used in our study was 700/100 000 (Washington *et al.* 1984). Some of this difference may be explained by the different racial composition of the populations, in the United States study non-white women had rates 2·5 times those of white women. However, it seems likely that differences in risk factors such as sexual behaviour and contraceptive use may contribute to a higher incidence of the disease in Northern America, and criteria for diagnosis and hospital admission may also be different.

Pelvic inflammatory disease is an important public health problem and may have tragic sequelae for the women concerned (Westrom 1975, 1980). If the rising trends noted here reflect a true increase in the incidence of this disease there will also be important implications with respect to future demand for hospital services particularly for treatment of infertility.

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Neonatal thyrotrophin and mode of delivery

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Summary. This study was performed to assess the association between labour and the mode of delivery with the umbilical cord plasma thyroxine (T4) and thyroid-stimulating hormone (TSH) concentrations in full-term uncomplicated pregnancies delivered in our hospital. Babies born vaginally had statistically significantly higher umbilical cord plasma TSH but similar T4 concentrations than babies born by caesarean section. Labour was not associated with either higher TSH or T4 concentrations. All the babies with an elevated TSH concentration (>20 miu/l) were born vaginally. Our findings indicate that the mode of delivery should be taken into consideration in the interpretation of umbilical cord plasma TSH results.

Screening for congenital hypothyroidism by measuring umbilical cord plasma thyroxine (T4) and thyroid-stimulating hormone (TSH) has now become an established practice (Fisher *et al.* 1979; John 1987). Because of the relatively wide range of T4 concentrations in the umbilical cord plasma, TSH has been suggested as a more reliable index variable (Walfish 1976). Whereas the diagnosis is easy if an elevated TSH concentration is associated with a low T4 concentration, it is less certain if the latter is normal, as the TSH concentration may return to normal after a few weeks, or increase further with a falling T4 concentration (John 1987). Our recent study (Lao & Panesar 1989) examining the association between mode of delivery and cortisol concentrations in cord blood revealed higher concentrations in babies born vaginally. In the same light we wondered if the stress of labour and delivery would be associated with an elevation of TSH concentration in addition to the TSH surge which is a common phenomenon in newborn infants. The present study was conducted to look at the relation between the mode of delivery and the cord blood T4 and TSH concentrations, which are now routinely measured for every baby born in our hospital as the screening test for congenital hypothyroidism.

Patients and methods

In a retrospective survey, four groups of babies born during a 2-month period were selected according to the mode of delivery. The first group (A) comprised those who had a normal spontaneous vaginal birth ($n = 59$) of whom 30 (51%) were born after the mother had received epidural analgesia in labour; the second group (B) comprised babies born by forceps for indications other than fetal distress ($n = 31$); the third group (C) comprised those who had been born by elective caesarean section ($n = 43$); and the last group (D) included babies born by emergency caesarean section after their mother failed to progress in labour ($n = 48$). All the babies were singletons and had been born at term without any complications, such as neonatal asphyxia, birth trauma or congenital malformations. The mothers did not have any obstetric or medical complications. The exclusion of babies associated with obstetric, medical and perinatal complications should remove other possible

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Table 1. Umbilical cord plasma T4 and TSH concentrations, birthweights and mode of delivery

	Vaginal delivery		Abdominal delivery		
	Spontaneous Group A (n = 59)	Instrumental Group B (n = 31)	Elective Group C (n = 43)	Emergency Group D (n = 48)	Normal range
Birthweight (g)	3320 (330)	3170 (348)	3333 (326)	3368 (474)	
T4 (nmol/l)	108·1 (20·8)	112·5 (19·9)	107·8 (18·6)	109·7 (25·5)	73–157
TSH (miu/l)	9·0 (6·3)	11·7 (10·3)	4·8 (2·2)	4·6 (2·7)	0–20

Results are mean (SD) values. t-test $^*P<0{\cdot}001$.

confounding factors so that the association between labour and the mode of delivery with umbilical cord plasma T4 and TSH concentrations could be analysed. The number of babies in groups B, C and D were arrived at after exclusion of the forementioned complications, and the sample size in group A was chosen so that the numbers with and without epidural analgesia were similar. The number of mothers in groups B, C and D who received epidural analgesia was 10, five and eight respectively.

The results of the umbilical cord plasma T4 and TSH, measured by radioimmunoassay in batches using Syva EMIT and Diagnostic Products Corporation kits respectively, were retrieved from the laboratory, and analysed according to the mode of delivery. Student's t-test and Fisher's exact probability test were used for statistical analysis where appropriate.

Results

The mean birthweight, T4 and TSH concentrations in the four groups are shown in Table 1. In group A, there was no statistically significant difference in the mean TSH concentration between the babies whose mothers had received epidural analgesia (9·7, SD 5·9 miu/l) and those whose mothers had not (8·4, SD 6·7 miu/l), with the values of the latter having the same range and distribution as the former. Therefore, the influence of epidural analgesia on hormone concentrations was considered negligible in the subsequent analysis. Groups A and B both had significantly higher TSH concentrations ($P<0{\cdot}001$) than either group C or D, but the TSH concentration was similar in groups A and B, as well as in groups C and D. There were no significant differences in the birthweight or T4 concentration between groups A, B, C and D. The TSH and T4 levels in all groups are shown in Fig. 1.

The route of delivery was statistically significantly associated with TSH concentration in cord blood, as all nine babies with raised TSH (>20 miu/l) were born vaginally (groups A and B) compared with none of the babies born by caesarean section (groups C and D) ($P = 0{\cdot}0015$, Fisher's exact probability test, Table 2). Further analysis showed that although in group B the frequency of raised TSH was three times the rate in group A (19% *vs* 7%), this difference was not statistically significant ($P = 0{\cdot}058$, Fisher's exact probability test). However, the route of delivery was not similarly associated with difference in T4 concentrations (Table 2). None of the newborn babies with raised TSH was found to be hypothyroid subsequently.

Discussion

In the human fetus, gestational age is probably the most important physiological factor to influence TSH concentration. An abrupt increase in serum TSH occurs around 18–22 weeks gestation, from a previously low concentration to one

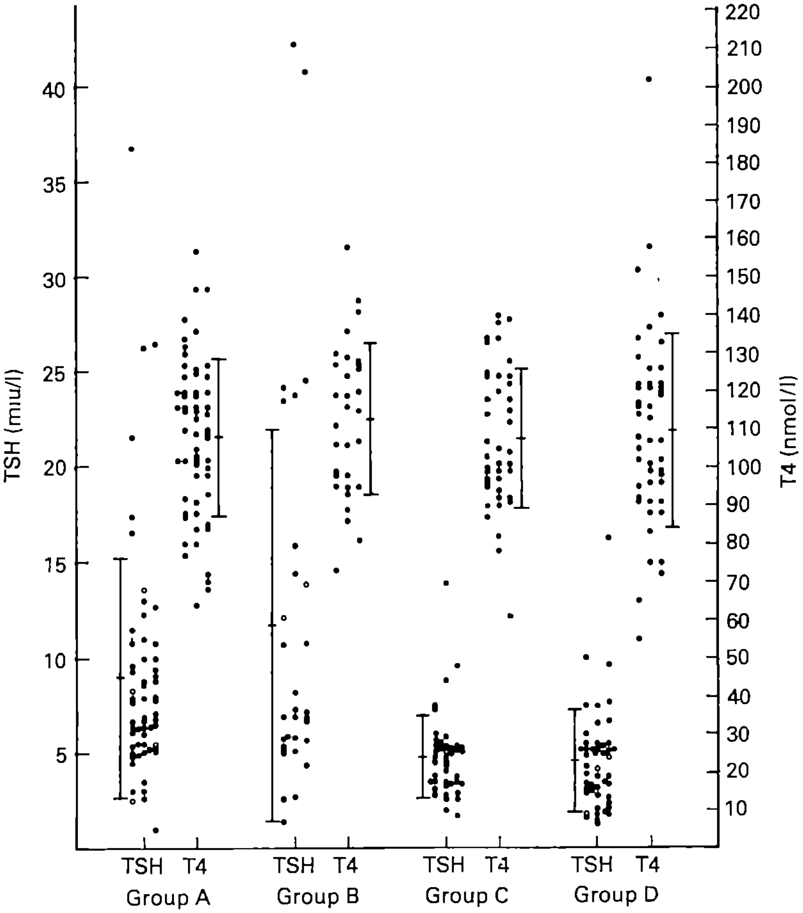

Fig. 1. Umbilical cord plasma T4 (●) and TSH (○) concentrations according to mode of delivery. Group A: spontaneous vaginal delivery; group B: instrumental vaginal delivery; group C: elective caesarean section; group D: emergency section for failure to progress. Vertical bars beside actual values indicate the mean ± SD.

similar to that found in mature newborn (Fisher *et al.* 1970). This may account for the lack of difference in TSH concentrations between preterm and term infants (Athanasiadis *et al.* 1981). However, neonatal TSH concentration appears not to be influenced by the plasma concentration of thyroid hormones, as there was no correlation between TSH and T4 or tri-iodothyronine in the normal newborn (Byfield *et al.* 1979), and the postnatal surge in TSH is not fully suppressed by a higher plasma concentration of T4 (van Herle *et al.* 1975; Lightner *et al.* 1977).

Other factors might also influence neonatal TSH concentration. Methodological problems may give an apparently raised neonatal TSH concentration. This could be due to antibodies interfering with the assay (John 1987), which would also give a similarly high TSH concentration in the maternal circulation (Lazarus *et al.* 1983), or to heterophilic antibodies against rabbit Ig if rabbit antibodies are used in the TSH assay (Hedenborg *et al.* 1979).

The most common yet most poorly reported cause for raised TSH in the normal newborn is probably the stress of parturition and asphyxia.

Table 2. Number (%) of high values of T4 and TSH according to route of delivery

	Vaginal (n = 90)	Abdominal (n = 91)	Fisher's test
T4 >157 nmol/l	1(1%)	2(2%)	NS
TSH >20 miu/l	9(10%)	0(—)	P=0·0015

Walfish (1976) noted that 9·4% and 0·24% of the population he studied had cord serum TSH concentration greater than 40 and 50 μ-units/ml respectively, and that seven of nine babies with TSH above 50 μ-units/ml were found to be normal subsequently, i.e. 78% false-positive results. Whereas information about delivery was not available for six of the babies, the seventh, with a TSH of 142 μ-units/ml, was born by high forceps which resulted in a scalp laceration and a low Apgar score, suggesting that extreme parturition stress and hypoxia can result in a high TSH concentration. This might also account for the three babies with an unexplained raised TSH (>50 miu/l) out of a total of seven who were not hypothyroid in the review by John (1987).

In our study, the values of both T4 and TSH were generally within the normal range in all the babies. The TSH concentration was similar in babies born by elective caesarean section and intrapartum emergency caesarean section, suggesting that labour *per se* was not associated with a higher neonatal TSH concentration. However, in the vaginal delivery groups, two TSH results were between 40 and 50 miu/l. Our results suggest that the route of delivery rather than the presence of labour is associated with different levels of the cord serum TSH concentration, even in full-term appropriate-for-gestational-age and non-asphyxiated infants, and that instrumental delivery is more strongly associated with higher TSH levels than spontaneous delivery. Perinatal asphyxia could have caused the extreme elevation of cord TSH concentration in one infant reported by Walfish (1976).

The results of this study indicate that the route of delivery is significantly associated with the cord blood TSH concentration. Although TSH estimations provide a more specific screening test for congenital hypothyroidism, a high false-positive rate may be found if the route of delivery is not taken into account. If, to avoid this difficulty, a high cut-off for TSH concentration is used, a certain proportion of infants with hypothyroidism may be missed since immaturity of the hypothalamic-pituitary-thyroid axis may cause a lack of elevation of TSH (Grant *et al.* 1986). The additional discrimination that can be provided by the measurement of neonatal serum thyroglobulin concentration (Osotimehin *et al.* 1978), or the TSH level on day 5 of life (Delange *et al.* 1977) may be required. Thus the simultaneous measurement of cord blood T4 concentration still has a place in the screening of congenital hypothyroidism.

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Ligneous conjunctivitis involving the cervix. Case report

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Case report

A 23-year-old nulliparous woman was examined in the colposcopy clinic at the Royal Northern Hospital, London, in January 1987. She had had a persistent and intermittently offensive vaginal discharge for 3 years. The discharge was blood-stained after intercourse and sometimes contained small pieces of tissue. Apart from dysmenorrhoea her menstrual cycle was normal. She had been trying to conceive without success for 2 years. At the age of 18 years incision drainage of a haematocolpos had been necessary, although this had not caused discomfort before the operation. Otherwise she was in good health.

During the 3 years before the colposcopy, the patient had seen numerous specialists in an attempt to rectify the discharge. Each time examination had revealed a necrotic, fibrinous, exophytic growth obscuring most of the cervix and posterior fornix (Fig. 1). Microbiological and virological investigation had failed to detect a significant pathogen, and histological examination had consistently shown stratified squamous mucosa with ulceration and eosinophilic fibrinous material. There was an inflammatory cell infiltrate and no evidence of malignancy.

Of note in her past medical history was that she had suffered from a persistent membranous conjunctivitis during the first 3 years of life and had received in-patient care at Great Ormond Street and Moorfields Eye Hospitals in London.

Colposcopic assessment at our hospital revealed identical findings to her previous consultations. Bimanual examination was essentially normal apart from superficial ulceration in the region of the growth. General examination did not reveal any other abnormality.

Due to the persistent nature of this benign lesion, removal was attempted by carbon dioxide laser vaporization. This resulted in improvement in menstrual discomfort but vaginal discomfort and postcoital bleeding persisted. Colposcopy shortly afterwards demonstrated recurrence of the lesion. In March 1988 a further attempt was made to eradicate the lesion. The affected area was vaporized to 2–3 mm and a small cone biopsy removed to a depth of 8 mm.

Histologically the cone biopsy showed extensive loss of the surface epithelium and massive deposition of amorphous eosinophilic material. There was some surviving epithelium at the edges of the deposits and here the material was in a subepithelial location (Fig. 2). Deep to the deposits were many foreign body type giant cells, most of them containing brown material, presumably debris from previous laser treatment. The deposits did not stain with the Congo red and Thioflavine T stains for amyloid and Martius scarlet blue for fibrin.

Immunocytochemistry showed positive staining for fibrinogen and negative staining for cytokeratin. There was no staining for kappa or lambda light chains in the deposits, and a group of plasma cells in the cervix showed polyclonal staining.

Having failed to produce significant change with two locally destructive procedures, further surgical intervention seemed unlikely to be helpful. A dermatological opinion was sought in order to look into the possibility of a more wide-

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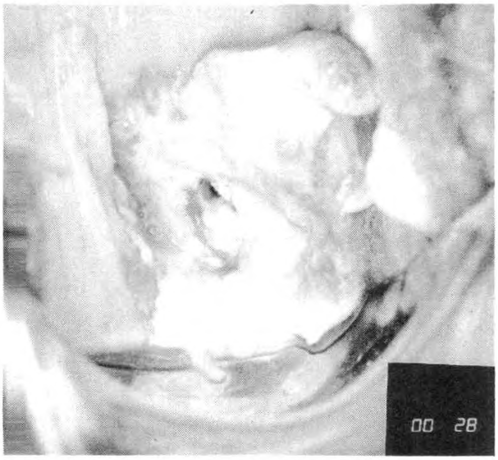

Fig. 1. Colposcopic view of vaginal exophytic growth.

spread mucocutaneous disorder. Two small fibrinous plaques on the gingival mucosa were biopsied and histologically showed similar appearances to the cervix with eosinophilic material deposited subepithelially. There was no surface ulceration and no giant cells present. The staining characteristics of the material were identical to that from the cervix.

Moorfields Eye Hospital was then contacted to determine the precise nature of her conjunctivitis in 1967. After consultation, it was realized retrospectively that the diagnosis in 1967 had been ligneous conjunctivitis and that she was now suffering from extra-ocular manifestations of the same disease.

Discussion

Ligneous conjunctivitis is a rare form of chronic membranous conjunctivitis of unknown aetiology (Hidayat & Riddle 1987). The disease usually begins in childhood but may be seen in adult or elderly patients. There are two phases to the disease. The first is an acute phase in which systemic manifestations such as fever, otitis media, sinusitis, vulvovaginitis, cervicitis and upper respiratory and urinary tract infections occur together with ocular disease. This is followed by a chronic phase during which there is recurrence of conjunctival lesions and, in a few patients, disease involving mucous membranes in other parts of the body. The ocular disease consists of involvement of either tarsal or bulbar conjunctivae by white, yellow or red firm masses which are either sessile or pedunculated. These may be associated with a mucoid discharge, inflamed red eye and impairment of vision. Histologically there are subepithelial deposits of

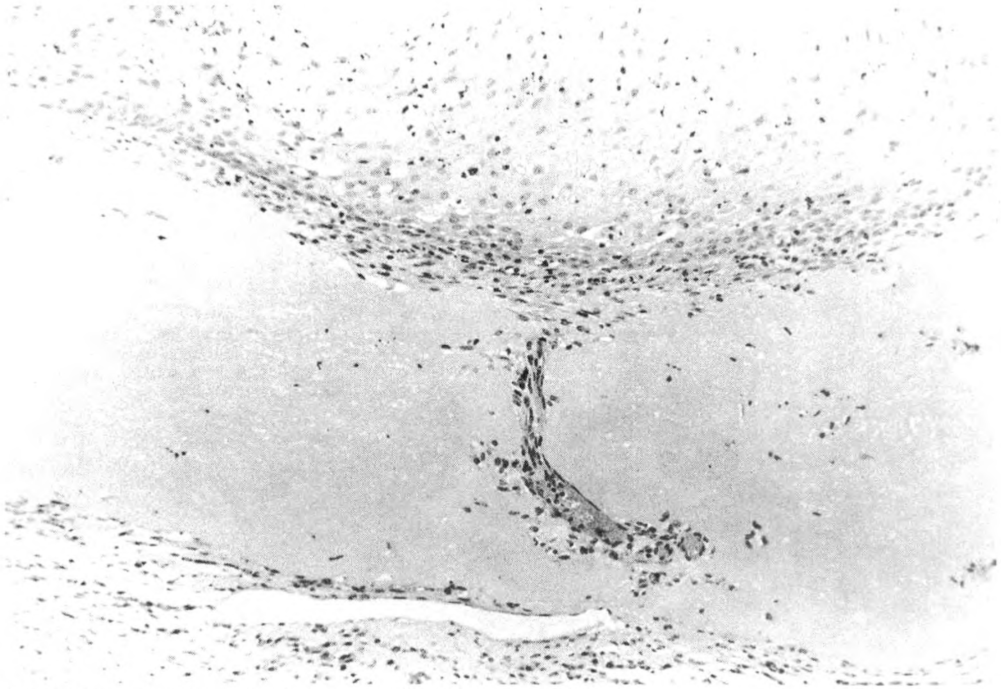

Fig. 2. Cervix showing amorphous subepithelial deposit. ×80.

amorphous eosinophilic material with foci of ulceration. Treatment is generally unsuccessful, surgical excision being followed by rapid recurrence. Cryotherapy, cautery, silver nitrate application, chymotrypsin, topical hyaluronidase and corticosteroids are all ineffective.

Chronic extra-ocular disease may produce similar lesions in the upper respiratory tract resulting in stridor and upper respiratory tract obstruction (Cohen Tervaert *et al.* 1986). There are at least two previous reports of ligneous conjunctivitis involving the cervix and vagina. In one of these a vaginal smear contained atypical cells suggestive of malignancy but a biopsy showed the features of ligneous conjunctivitis.

Extra-ocular disease may occur many years after the initial presentation with conjunctivitis. Our patient developed gynaecological symptoms 15 years after her initial presentation with conjunctivitis. Great difficulty was encountered in reaching a diagnosis despite wide consultation, and the patient underwent several unsuccessful attempts at treatment. The case remained unexplained until investigation into her ophthalmic records was made. Most gynaecologists are unfamiliar with this diagnosis. Pathologists with wide experience in gynaecology are unaware of this disease and it is not described in any of the standard reference textbooks on gynaecological pathology. The histology of the lesions is characteristic and a diagnosis can be made quite easily once it has been considered.

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SHORT COMMUNICATIONS

Thrombocythaemia and recurrent miscarriage

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The incidence of thrombocythaemia (a platelet count $>600\times10^9$/l) in a 10-year survey was 7 per 10^6 population per year (R. M. Pettit, personal communication). It is generally a disease of late middle age, but a second population of young and mainly female patients has been described (Hoagland & Silverstein 1978). An increased platelet count can be secondary (after splenectomy, associated with inflammation, malignancy or iron deficiency) or due to a primary myeloproliferative disorder. We describe four patients in whom a series of miscarriages before 20 weeks gestation appears associated with thrombocythaemia and estimate the prevalence of this association in patients with unexplained repeated miscarriage.

Patients and results

Routine screening of women attending miscarriage clinics with a history of unexplained recurrent miscarriage revealed four patients with thrombocythaemia, detailed in Table 1. A diagnosis of myeloproliferative syndrome was made in three by exclusion of known secondary causes for an elevated platelet count accompanied by bone marrow findings compatible with this diagnosis. These patients were all Philadelphia chromosome negative.

In each case, the significance of an elevated platelet count had not been considered previously, although such a report was available from previous medical records. All miscarriages were in the first trimester except for two (at 19 and 20 weeks for patient four), and placental pathology had not been obtained. These patients had not acquired antibodies directed against paternal lymphocyte antigens, and established cytogenetic, endocrine, gynaecological or other medical causes that may contribute to recurring early fetal loss had been excluded through diagnostic testing (Johnson *et al.* 1988; Smith & Cowchock 1988). These four cases form part of a series of 600 couples referred to the University of Liverpool Medical School or Jefferson Medical College for immunological investigation or treatment of recurrent miscarriage. Thus, the prevalence of overt thrombocythaemia among these women with three or more consecutive miscarriages was 0·7% (95% CI 0·2 to 1·8%), significantly higher than figures for the general population.

Platelet aggregation studies were performed in patients 1 and 2 with the patients stabilized initially on 80 mg aspirin daily. Platelet aggregation to ADP, collagen, ristocetin and adrenaline was measured using standard optical density techniques. This dose of aspirin did not completely abolish aggregation to ADP (final concentration 5 μmol/l) or collagen (final concentration 4 μg/ml). Aggregation responses to these two antagonists were, however, essentially abolished when aspirin was given at a higher dose of 80 mg every 8 h. One of these women (no.1) was treated with 80 mg aspirin daily in a fourth, chromosomally normal, pregnancy which ended again in miscarriage. Another patient (no.3), with primary myeloproliferative syndrome, achieved and maintained a platelet count within the normal range following a short course of chemotherapy;

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Table 1. Patient summary

Patient	Gravidity/ parity	Platelet count on initial investigation ($\times 10^9$/l)	Primary diagnosis	Complicating conditions
1	G3 P0	870	Myeloproliferative syndrome	None
2	G7 P0	1130	Myeloproliferative syndrome	Splenic infarction
3	G6 P0	1250	Myeloproliferative syndrome	None
4	G5 P0	700	Ulcerative colitis	None

she conceived within 6 months of treatment and had an uncomplicated pregnancy resulting in the birth at term of a healthy 4·12 kg male infant.

Discussion

Pregnancy associated with thrombocythaemia has been described previously (Okayasu *et al.* 1981; Kaibara *et al.* 1985; Ferrari *et al.* 1986; Snethlage & Ten Cate 1986; Belluci *et al.* 1986; Falconer *et al.* 1987; Jones *et al.* 1988; Mercer *et al.* 1988). Four affected women had an uncomplicated pregnancy without treatment; most had a history of miscarriages, placental infarctions or preterm delivery. After treatment with aspirin, dypyridamol, aspirin with dypyridamol and heparin, heparin alone, or plateletpheresis, seven patients with previous losses had liveborn children. Another treated pregnancy was complicated by pre-eclampsia and placental infarctions. Despite these case reports, an elevated platelet count is not generally considered as a possible cause of unexplained miscarriage or stillbirth. Attention should therefore be paid to laboratory reports of elevated platelet counts in patients with unexplained pregnancy losses.

Essential thrombocythaemia in young persons can generally be a benign disorder, although not without risk of haemorrhage or thrombosis (Hoagland & Silverstein 1978). It appears to be associated, however, with an increased risk for pregnancy loss. The reports cited above suggest that such losses might be prevented by treatment with antithrombotic agents or by lowering the platelet count. If aspirin is used, it is likely that higher doses will be needed than the daily paediatric tablet generally recommended in pregnancy disorders such as those associated with anti-phospholipid autoantibodies. We have shown in platelet aggregation studies that 80 mg aspirin daily failed to demonstrate the expected block in cyclo-oxygenase activity, whereas this was blocked by 80 mg given every 8 h.

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Fetal alpha-fetoprotein concentration in growth retardation

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Raised maternal serum alpha-fetoprotein (AFP) in the absence of fetal malformations has been associated with adverse pregnancy outcome such as low birthweight and intrauterine growth retardation (IUGR) (Nelson *et al.* 1987). Although impaired placental function predisposing to fetomaternal haemorrhage is the suggested mechanism (Brock *et al.* 1980), increased fetal production is another possibility.

We have recently reported a normal range for fetal serum AFP concentration with gestation (Nicolini *et al.* 1988). In this study we measured AFP in 30 fetuses (26–36 weeks by certain dates and confirmed by scan before 20 weeks) with ultrasound measurements of biparietal diameter and abdominal circumference <5th centile for gestational age. Birthweight was <5th centile in all Umbilical artery blood flow velocity waveforms showed end-diastolic frequencies (EDF) in 12 fetuses whereas 18 showed absent EDF. Fetal blood sampling was performed under ultrasound guidance as part of clinical management for the determination of fetal karyotype and acid-base status. Fetal AFP was assayed on sera which had been stored for 1–6 months at −20°C. Results were expressed by gestational age. As fetal serum AFP declines linearly with gestation ($y = 3312{\cdot}3 - 97{\cdot}7\,x$; $r = 0{\cdot}84$, $P<0{\cdot}001$) (Nicolini *et al.* 1988) and as this may be related to increasing fetal size, results were also expressed as a function of estimated fetal weight (Hadlock *et al.* 1983), in order to correct for the smaller size of fetuses with suspected IUGR. Maternal serum AFP was not measured because of the absence of a normal range over the second half of gestation in our hospital.

Fetal AFP was within normal limits for gestation in 22 of 30 fetuses with IUGR (10 of the 12 with EDF and 12 of the 18 with absent EDF). As shown in Fig. 1, the distribution of fetal AFP concentration in the 30 IUGR fetuses was evenly scattered around the mean. When plotted as a function of estimated fetal weight, AFP concentration was below the lower limit in 16 of 30 fetuses with similar proportions in those with EDF (5 of 12) and those with absent EDF (11 of 18, $\chi^2 = 1{\cdot}094$, $P = 0{\cdot}3$). A positive linear correlation between $P\mathrm{o}_2$ and fetal AFP when expressed as multiples of the mean for fetal weight ($r = 0{\cdot}42$, $P = 0{\cdot}02$) implies lower fetal AFP with increasing severity of IUGR. However, this correlation was no longer significant when AFP was expressed as multiples of the mean for gestational age.

Thus, our results do not support a fetal basis for the increased levels of maternal serum AFP reportedly associated with IUGR. The increase seems more likely to be due to increased transplacental passage possibly related to abnormal placental function. Fetal AFP in IUGR is not only normal for gestational age but is even reduced when related to fetal size. Indeed decreased transplacental transport of amino acids (Dicke & Henderson 1988) and altered hepatocyte function (Cox *et al.* 1988) have been found in IUGR. However, the low fetal serum AFP in IUGR fetuses when compared with normals of the same size, is better explained by differences in gestational age given decreasing

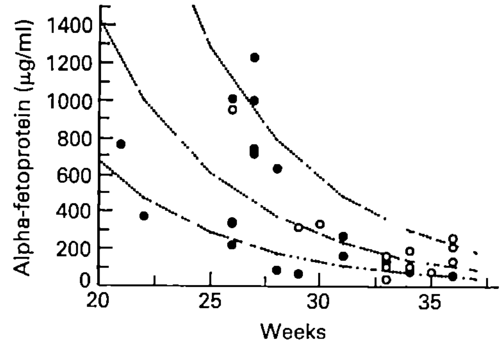

Fig. 1. Serum alpha-fetoprotein (AFP) values plotted against gestational age in growth-retarded fetuses with absent end-diastolic flow (●) and those with end-diastolic flow (○). Normal range for gestation is expressed as logarithmic mean and 95% data intervals (± 1·96 SD).

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AFP with advancing gestation. Therefore gestational age rather than size is the determinant of fetal serum AFP.

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Outcome of labour in occipitoposterior positions in an African population

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In tropical Africa, contracted pelvis is common (Lister 1960; Mtimavalye *et al.* 1974; Briggs 1983). Racial factors, malnutrition and infections in infancy are some of the factors thought to be responsible for the frequency of this problem. In addition, teenage marriages, and thus teenage pregnancies, are encouraged or condoned in several parts of Africa. This results in the young immature woman having babies when the pelvis is not fully grown (Effiong & Banjoko 1975; Harrison *et al.* 1985). Occipitoposterior positions result in an increase in the presenting diameter of the fetal skull because of the associated attitude of deflection. In an environment such as tropical Africa where contracted pelvis is common, this malposition may be associated with considerable maternal morbidity. This short report sets out the results of a prospective study of labour associated with the occipitoposterior positions.

The study group comprised 100 consecutive pregnant women at term (37–41 weeks gestation) who arrived in labour (regular uterine contractions) at the Ahmadu Bello University Hospital, Zaria, Nigeria, with cervical dilatation of ≤6 cm and with live singletons presenting by the head in an occipitoposterior position. All had attended the antenatal clinic. A comparison group of 100 women was formed comprising the women admitted in labour directly after the delivery of each study woman, with a live singleton fetus, and who matched her age, height and parity, but with an occipito-anterior or transverse position. Women with eclampsia and antepartum haemorrhage were excluded, as in these conditions delivery is normally expedited once the diagnosis is made. Labour was augmented by oxytocin infusion in 15 women in the study group and in seven in the comparison group and managed along conventional lines involving the recording of fetal heart rate, maternal vital signs and uterine contractions. In addition, the time, mode of delivery and fetal outcome were noted.

The mean age of the women was 22 years, 20% were very young (<16 years); the mean height was 1·55 m, 34% were <1·53 m and only 11% were >1·63 m. The average parity was between 2 and 3 and 52% were having their first baby. The duration of labour, position of fetal head, mode of delivery and birthweight are shown in Table 1.

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Table 1. Position of fetal head, duration of labour, mode of delivery and birthweight in the two groups

	Study group (n=100)	Comparison group (n=100)
Position of fetal head		
LOP	32	0
DOP	8	0
ROP	60	0
ROT	0	20
ROA	0	8
LOA	0	46
Duration of labour (h)		
<12	24	48
12–24	37	42
>24	39	10
($P<0{\cdot}005$)		
Mode of delivery		
Spontaneous vaginal occiput-anterior and low cavity forceps	43	88
Difficult operative vaginal midcavity and rotational forceps	11	3
Caesarean section	32	9
Spontaneous face to pubes	14	0
($P<0{\cdot}001$)		
Birthweight (g)		
<2500	5	2
2500–3500	74	86
>3500	21	12
Mean (SD)	3157 (456)	3151 (414)

As judged by the duration of labour, injuries to birth canal and fetal outcome, labour was easiest in the spontaneous face to pubes group. Women who gave birth spontaneously when the fetal occiputs had rotated anteriorly and those who had a low cavity forceps extraction also had easy deliveries. None of the women in the comparison group gave birth to an infant that was face to pubes. In both groups, caesarean section was associated with such dystocia that vaginal delivery was deemed impossible.

Maternal age, parity and stature had a marked influence on the mode of delivery. Young primiparous women of short stature generally had difficult labours which were often terminated by caesarean sections. Caesarean section for dystocia was necessary about four times more often in the study group than in the comparison group. On the whole, labour outcome was best in the women who were aged between 20 and 29, of average or tall stature (>1·53 m) and having their second, third or fourth babies. Those who were delivered with the fetus face to pubes were generally multiparous, in their twenties and over 1·62 m tall.

Sixty-two women in the study group and 83 in the comparison group returned home within 24 h of delivery. Of the rest, the most serious puerperal complication was genital tract or wound infection in 25 women in the study group and 6 women in the comparison group. Two women died, both from the study group, from septicaemia and anaesthetic complications.

There were no stillbirths or immediate neonatal deaths in the two groups. Five low birthweight babies (<2500 g), all in the study group, were born by caesarean section.

Discussion

The degree of unfavourable outcome of malpositions in Africans as shown by this report is in excess not only of what would be expected of their white European counterparts (Chalmers 1968), but also in comparison with their fellow African women. Major complications were more commonly encountered and the need for caesarean section was high. The fact that all the low birthweight babies were born in the study group by caesarean section would suggest that the disproportion responsible is due to the maternal pelvis being inadequate.

The implication of this study for obstetric care in Africa is obvious. Because malpositions tend to have a more unfavourable outcome in Africans, maternity centres should be supervised by persons capable of recognizing early occipitoposterior positions and associated delay in labour. Such women could then be transferred to the care of a team with the capacity to perform caesarean section.

Acknowledgment

This work is part of a larger study entitled ‘Occipitoposterior positions: Predictive indices on the outcome of labour’ for which the University of Lagos has awarded the MD degree.

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Plasma lipid risk factors in oophorectomized women

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Premenopausal women suffer less from coronary heart disease (CHD) than do men (WHO 1982) and it has been suggested that this sex difference is due to the protective effect of oestrogen. We have investigated the changes in plasma lipid risk factors for CHD associated with bilateral oophorectomy in premenopausal women.

Patients and methods

We studied nine women (median age 45·5 years, range 39–50 years) about to undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy for benign uterine fibroids. Premenopausal status was confirmed by regular menstruation and by oestrogen and gonadotrophin levels within appropriate normal ranges. The women had not taken hormonal therapy for 3 months before oophorectomy and were <120% of their ideal body-weight. Each subject acted as her own control, being seen both before and 6 weeks after oophorectomy. No hormones or other medications were given during this period and the women were requested not to change their diet. Oestradiol replacement therapy was started after the second visit. Approval for the study was obtained from the ethics committee.

At each visit, EDTA plasma was obtained after an overnight (12–14 h) fast. Samples for hormone, lipid and lipoprotein analysis were stored at 4°C and analysed within 4 days; samples for apolipoprotein assays were stored at −20°C.

Chemical assays

Oestradiol, FSH and LH levels were determined by radioimmunoassay. Plasma and lipoprotein cholesterol and plasma triglyceride concentrations were measured by fully enzymatic assays. High-density lipoprotein (HDL) and HDL subfraction cholesterol were measured using heparin/manganese (Warnick & Albers 1978) and dextran sulphate (Gidez *et al.* 1982) precipitation methods. Low-density lipoprotein (LDL) cholesterol was calculated (Friedewald *et al.* 1972). Within- and between-batch coefficients of variation were <5% except for HDL subfractions (<10%). Apolipoproteins (apo) AI, AII and B were measured in a single batch by 'rocket' immunoelectrophoresis (Laurell 1972); the within-batch coefficient of variation was <3%.

Results

No significant changes in body-weight were observed. Plasma oestradiol levels fell from mean (SD) 194 (134) pmol/l to <50 pmol/l. Mean (SD) plasma FSH and LH levels rose from 13·7 (14·2) and 8·0 (5·6) units/l, respectively, to

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Table 1. Plasma lipids, lipoproteins and apolipoproteins in nine women before and after bilateral oophorectomy

	Pre-oophorectomy	Post-oophorectomy
Total cholesterol (mmol/l)	5·3 (3·5–7·1)	5·6 (3·9–7·1)
Triglycerides (mmol/l)	0·8 (0·3–1·9)	1·4 (0·4–3·1)*
LDL cholesterol (mmol/l)	3·3 (1·5–5·2)	3·4 (1·6–4·7)
HDL cholesterol (mmol/l)	1·7 (1·0–2·0)	1·8 (0·9–2·1)
HDL2 cholesterol (mmol/l)	0·3 (0·1–0·8)	0·4 (0·2–0·7)
HDL3 cholesterol (mmol/l)	1·4 (0·8–1·6)	1·5 (0·7–1·7)
Apolipoprotein AI (g/l)	1·1 (1·0–1·3)	1·1 (0·9–1·3)
Apolipoprotein AII (g/l)	0·3 (0·2–0·7)	0·3 (0·2–0·7)
Apolipoprotein B (g/l)	0·7 (0·2–1·2)	0·7 (0·2–1·3)

Values are presented as median (range). *Significantly different from pre-oophorectomy value (Wilcoxon ranked-pairs test).

>40 units/l. These levels are typical of the postmenopausal state.

Plasma total and lipoprotein cholesterol levels were unaffected by oophorectomy (Table 1). Apolipoprotein markers for LDL (apoB) and HDL (apoAI and apoAII) were similarly unchanged. Plasma triglycerides increased by 60% within 6 weeks.

Discussion

Oophorectomy was not associated with changes in established CHD risk markers, such as LDL or HDL cholesterol, or apolipoproteins, which may be better indicators of risk (Thompson 1984). Although a larger sample size might have distinguished some of the minor differences as being statistically significant, these were of a magnitude which would have few implications for CHD risk. Plasma triglycerides increased, although the clinical significance of this is controversial (Hulley *et al.* 1980).

The belief that loss of 'protective' oestrogen at the menopause causes the loss of the sex difference in CHD incidence has been challenged (Godsland *et al.* 1987) on the grounds that major epidemiological studies differ as to whether the menopause increases CHD incidence (Gordon *et al.* 1978; Colditz *et al.* 1987). Furthermore, the diminution in the sex difference in CHD incidence seen in national mortality data may be equally ascribable to an age-related deceleration in incidence in men (McGill & Stern 1979). Studies of CHD incidence in oophorectomized women have failed to demonstrate the presence or absence of a link (Roberts & Giraldo 1979) although more recent epidemiological surveys do suggest an association (Gordon *et al.* 1978; Colditz *et al.* 1987). The effect on lipid risk factors, the candidate mechanism by which sex may affect CHD incidence, is also controversial. Most cross-sectional studies show higher total and LDL cholesterol levels in castrates than in age-matched intact control subjects (Higano *et al.* 1959; Oliver & Boyd 1959; Ritterband *et al.* 1963) although this has been disputed (Manchester *et al.* 1971) and is not supported by prospective studies.

Punnonen & Rauramo (1976) found increased triglycerides, but not total cholesterol, in women 1 month after oophorectomy, returning to baseline within 6 months. In a later study Punnonen & Rauramo (1980) reported that HDL was unchanged by oophorectomy. Neither study measured LDL. Pansini *et al.* (1984) found no change in triglycerides, but an increase in total cholesterol after 2 months, apparently due to increased HDL. This increase—the opposite to that expected—followed an initial decrease.

Taken together, these results do not suggest that oophorectomy induces changes in plasma lipid risk factors which would predispose to CHD. The elevated triglyceride levels seen in our study may be transient (Punnonen & Rauramo 1976), perhaps reflecting changes in diet or activity after surgery. The identification of long-term effects of oophorectomy on plasma lipid risk factors will be hindered by the need for hormone replacement therapy in such women.

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Hydatidiform mole following in-vitro fertilization. Case report

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A 40-year-old woman with bilateral tubal block underwent a fourth treatment cycle for in-vitro fertilization and embryo transfer (IVF–ET). Ovarian stimulation was with clomiphene citrate, 100 mg/day from day 3 to 7 of the menstrual cycle, together with human menopausal gonadotrophin (hMG) from day 6 onwards of the cycle. Ovulation was triggered by the administration of 10 000 iu of human chorionic gonadotrophin (hCG) on day 10 of the cycle, and oocyte collection was performed 35 h later by laparoscopy. The husband produced a normospermic semen sample (volume 2 ml, sperm density 192×10^6/ml, 80% motility, 60% normal forms) 1 h before the laparoscopy. Motile spermatozoa were prepared by a conventional swim-up technique and adjusted to a concentration of 3×10^6/ml. Four mature oocytes were retrieved from six follicles at laparoscopy. Spermatozoa were added to the oocytes 5 h after the laparoscopy to give a final insemination concentration of 100 000 spermatozoa/ml. The oocytes were checked for signs of fertilization 18 h after insemination, and two pronuclei were found in each of the four oocytes. On the third day after oocyte recovery, three eight-cell embryos were replaced transcervically into the uterus using a Bourn embryo transfer catheter (Wallace, Colchester, UK). The luteal phase was supported with 2500 iu of hCG on the day of embryo replacement, as well as 2, 5, 8 and 11 days after replacement.

The concentration of urinary hCG was determined using immunochemical tests with sensitivities of 500 iu/l (Neo-Plantest Duoclon) and 2500 iu/l (Pregnosticon Planotest: both Organon Teknika). A continuous rise in hCG was found. An ultrasound scan of the pelvis at 6·5 weeks from the last menstrual period showed an irregular intrauterine gestational sac with no fetal echoes. The patient then attended weekly for repeat ultrasound scans and pregnancy tests. Clinically the uterus continued to increase in size corresponding with the period of gestation, with rising urinary hCG concentration, although this remained in the lower range of normal for the gestational age. The ultrasound scan continued to show an irregular gestational sac with few internal echoes appearing in it, but with no sign of a fetal heart.

The patient was admitted with vaginal bleeding at 9·5 weeks gestation. A repeat pregnancy test on the day of admission showed for the first time a sharp rise in urinary hCG concentration to a level well above that expected for the gestational age. An ultrasound scan showed the same picture as previously. A hydatidiform mole was suspected and with the woman's consent the uterus was evacuated under general anaesthesia using a sponge forceps and a sharp curette.

Pathological examination of the products of conception showed many chorionic villi to be vesicular with central degeneration and focal trophoblastic hyperplasia, confirming a diagnosis of a complete hydatidiform mole. The patient was counselled regarding her disease and was referred to the supra-regional centre for trophoblastic disease for follow-up. The level of hCG showed a sharp decline after the evacuation and remained low until the time of writing this report (10 months after the evacuation).

Discussion

The initial diagnosis of a hydatidiform mole is most effectively made using ultrasonography in combination with hCG measurement (Kohorn 1984). However, the value of the hCG determination is limited; whilst hCG concentrations in body fluids of women with molar pregnancy are usually higher than those associated with normal pregnancy, a proportion of women with a mole show urinary or serum hCG levels within the normal range for the appropriate stage of pregnancy (Bagshawe 1984). In our patient, urinary hCG titres, in the early stage of pregnancy, were approaching the lower limit of the expected normal range for a singleton pregnancy. However, the urinary output of hCG rose rapidly at the 10th week of pregnancy suggesting a large increase in hCG secretion at this time. If this is the case, careful consideration must be given to the stage of pregnancy when measuring hCG for diagnostic reasons. Surgical intervention prevented the further investigation of hCG output at a later stage of pregnancy.

A molar pregnancy after IVF–ET has been described previously by Wiswedel (1987), but it is difficult to compare with our report because we are not told whether it was a complete or partial mole and it was unclear whether the embryos transferred had only two pronuclei after insemination.

The formation of a complete mole after the transfer of embryos with two pronuclei is consistent with previous observations regarding the aetiology of molar pregnancies. The complete mole usually results from the fertilization of an oocyte by a single spermatozoon which is diploid or undergoes diploidization, with only about 4% of complete moles resulting from dispermic fertilization (Ohama *et al.* 1981). This means that most embryos which form complete moles could not have been identified at the time of post-fertilization assessment. Transfer of embryos with three pronuclei, which can be recognized, would be more likely to result in the formation of a partial mole (Lawler *et al.* 1982). Therefore, the examination of oocytes for the presence of pronuclei is unlikely to reduce the risk of a complete molar pregnancy. This is particularly important as the complete mole is the more dangerous, having the greater potential for malignancy (Kaufman 1988).

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting on 25 April 1989 at the Royal College of Obstetricians and Gynaecologists, London

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Distal urethral electric conductance (DUEC): a screening test for incontinent females? by A. B. Peattie, S. Plevnik & S. L. Stanton. Urodynamic Units, St James's and St George's Hospitals, London

The study seeks a less invasive test than cystometry to confirm incontinence objectively. Accurate detection of urinary leakage can be obtained by measurement of electric conductance in the distal urethra. Simultaneous recording of detrusor pressure and urethral electric conductance enables a correlation to be drawn between them. A short probe with two ring electrodes is placed in the distal urethra so that the electrodes record 1·5 cm from the external urethral meatus. Passage of urine past the electrodes causes a rise in their conductivity reading. The symptoms, cystometric findings and DUEC results of 115 women with incontinence are compared. Three patterns of urinary leakage can be identified during DUEC testing, which can be related to both symptoms and cystometric diagnosis. In patients with stress incontinence proven on cystometry, DUEC detected all cases but in addition picked up 20 extra patients from a group of 59. As DUEC only detects urinary leakage, cystometrically proven detrusor instability is detected if leakage occurs. Pick-up with DUEC does, however, enhance cystometric diagnosis as more provocation is used.

Obstetric outcome following the maintenance of epidural analgesia by continuous infusion compared to an intermittent regimen by D. Pinney, J. M. T. Pierce, A. Elias & R. F. Lamont. Department of Human Reproduction and Obstetrics, University of Southampton, Southampton

In a randomized study of 381 patients, 193 were allocated to an intermittent regimen and 188 to a continuous infusion for maintenance of epidural analgesia. Standard anaesthetic and obstetric protocols were used for all patients throughout the first and second stages of labour for each of the two methods. There was no difference between the groups with respect to age, parity, mode of onset of labour and indication for epidural analgesia. Maintenance of epidural analgesia by continuous infusion was better accepted by the women and resulted in a significantly decreased need for top-up doses. Hypotensive episodes were much fewer in the continuous group, as a result of which there were significantly fewer episodes of cardiotocographic abnormalities. The caesarean section rate in the continuous group was 12% compared to 16% in the intermittent group. It is concluded that the maintenance of epidural analgesia by continuous infusion is a safe and reliable method and may be more advantageous and less labour intensive than the traditional regimen.

Is it worth measuring oestrogens in women receiving gonadotrophin stimulant therapy? by P. Hardiman, M. Thomas, V. Osgood, V. Vlassopoulou & J. Ginsburg. Department of Endocrinology, Royal Free Hospital Medical School, Pond Street, Hampstead, London NW3 2QG

Ovarian responses to gonadotrophin therapy are conventionally monitored by urinary oestrogen or serum oestradiol (E_2). Compliance is poor since women dislike venepuncture as much as collecting urine. Although E_2 can be measured in saliva, this is rarely undertaken. With ultrasound, however, follicular development is assessed directly: we found ultrasound superior to urinary oestrogens for monitoring ovarian responses. Are oestrogens, therefore, still required for monitoring? We measured salivary and serum E_2 concurrently with ultrasound in 44 women during 82 gonadotrophin stimulated cycles. Salivary and serum E_2 correlated significantly with each other and with the number of follicles >1·0 cm but not with the number of *mature* follicles. The hMG manufacturers claim optimal ovarian responses with E_2 between 1100 and 3000 pmol/l, E_2>3000 indicating excessive stimulation so hCG should be withheld. However, in five cycles with only one or two mature follicles, E_2 was >3000 pmol/l; when we gave hCG, hyperstimulation did not ensue. Conversely in 13 cycles E_2 was 'optimal' but there were no mature follicles. Whilst spitting may be more acceptable than bleeding or urine collection, neither is as effective for monitoring gonadotrophin effects as ultrasound. When this is available, oestrogen assay provides no further useful information.

A cross-sectional study of platelet intracellular free calcium concentrations $P[Ca^{++}]_i$ throughout normal and hypertensive primigravid pregnancy by M. D. Kilby, F. Broughton Pipkin, S. Heptinstall* & E. M. Symonds. Departments of Obstetrics and Gynaecology, and *Medicine, Queen's Medical Centre, Nottingham NG7 2UH

The study included 48 pregnant women (12 in each trimester and 12 with pregnancy-induced hypertension (PIH)), 12 primiparous women at 6 weeks postpartum and 30 non-pregnant women. Basal demographic characteristics were similar in all groups. The platelet was used as a model of vascular smooth muscle. $P[Ca^{++}]_i$ was measured by the fura-2 method (assay coefficient of variation on triplicates 7·8%), using aspirin-treated platelets. $P[Ca^{++}]_i$ rose from 112·3 (SD 15·8) nM in the non-pregnant to 115·6 (SD 23·2) in the first, 120·1 (SD 19·7) in the second and 134·0 (SD 17·2) nM in the third trimester (P<0·01, ANOVA). $P[Ca^{++}]_i$ in the women with PIH was still further increased to 154·4 (SD 22·7) nM (P<0·02; by comparison with women in the third trimester). Concentrations had returned to basal (108·3, SD 23·5 nM) by 6 weeks postpartum. Total serum calcium decreased slightly throughout pregnancy from 2·44 (SD 0·17) mmol/l (non-pregnant) to 2·34 (SD 0·13) mmol/l (third trimester; not significant). The concentration in women with PIH was an identical 2·33 (SD 0·13) mmol/l. Several reports have appeared linking an increased $P[Ca^{++}]_i$ to increased arterial blood pressure in non-pregnant subjects. Our data suggest that the same may be true of PIH. Whether this is a primary or a secondary feature is not known.

Intrauterine pressures achieved during induction of labour with oxytocin and amniotomy compared with prostaglandin E_2 gel by S. Neave, G. C. Werkmeister, P. Hogston & R. F. Lamont. Department of Human Reproduction and Obstetrics, Princess Anne Hospital, Coxford Road, Southampton SO9 4HA

The ideal method for inducing labour artificially is that which most closely resembles spontaneous labour. Using an intrauterine catheter to measure intrauterine pressure, uterine activity integral recordings in the first stage of labour were made in 42 women induced by intravaginal prostaglandin E_2 (PGE_2) gel compared with 39 women induced by oxytocin and amniotomy and nine women in spontaneous labour. The two induction groups were well matched with respect to age, parity, indication for induction, gestational age and Bishop score. For a given rate of cervical dilatation, intrauterine pressures in the PGE_2 gel group were significantly less than in the oxytocin group. Similarly, the cumulative total of intrauterine pressures recorded to achieve a spontaneous vaginal delivery was significantly less in the PGE_2 gel group. When the uterine activity of the spontaneous labour group in the active phase of the first stage was compared with the two induction groups, the pressures achieved were found to mirror those of the PGE_2 gel group which was much less than the oxytocin group. In view of the increasing demand by women for natural childbirth and less medical intervention, intravaginal PGE_2 gel is likely to offer a welcome, more acceptable method for most women.

The effect of prostaglandin synthetase inhibitors on human pre-ovulatory follicular fluid prostaglandin, thromboxane and leukotriene concentrations by A. R. Priddy, S. R. Killick, M. Sullivan*, L. Patel* & M. G. Elder*. Departments of Obstetrics and Gynaecology, Withington Hospital, Manchester and *Hammersmith Hospital, London

Fifty-eight women requesting sterilization volunteered to take prostaglandin synthetase inhibitors (PGSI) before the operation which was timed by serial ultrasound examinations and human chorionic gonadotrophin levels (hCG) to be immediately pre-ovulatory. The protocol mimicked a previous study in Manchester where PGSIs induced luteinized unruptured follicles (LUF), i.e. prevented follicle wall rupture without affecting steroidogenesis, and was designed to test the hypothesis that LUF is the consequence of reduced intrafollicular eicosanoid concentrations. Overall, 5000 units of hCG were given intramuscularly when the mean dominant follicle diameter reached 18 mm and the operation was performed the next day. The volunteers were randomly ascribed to take a PGSI (indomethacin, azapropazone or bromfenac) or placebo from the time a follicle of 16 mm mean diameter was observed. The sterilization procedure allowed for the collection of follicular fluid for prostaglandin, thromboxane and leukotriene assay by RIA. Follicular fluid PGE$_2$, PGF$_{2\alpha}$ and LTB$_4$ were significantly reduced by bromfenac (the most potent PGSI) when compared with placebo. Follicular fluid PGE$_2$ and PGF$_{2\alpha}$ were also reduced by indomethacin. Azapropazone (the least potent PGSI) had no effect on eicosanoid concentration in the follicular fluid. None of the PGSI altered follicular fluid 6-keto PGF$_{1\alpha}$ or TXB$_2$ compared with placebo. The results show that intrafollicular prostaglandins and leukotrienes can be manipulated by oral therapy which could therefore be utilized to modify the ovulatory process in which these compounds are involved. Bromfenac would appear to be a potentially revolutionary non-hormonal oral contraceptive agent.

Receiver operating characteristic curves in obstetrics; the assessment of investigations in pregnancy-induced hypertension by A. C. J. Hutchesson, S. L. B. Duncan* & M. C. M. Macintosh*. The Royal Hallamshire Hospital and *The Jessop Hospital for Women, Sheffield

Clinical medicine aims to classify people as healthy or diseased; but most investigations produce results on a continuous scale, with frequent overlap of results from normal and diseased people. As a result, misclassification of some individuals occurs and can be quantified as true- and false-positive rates; these can be plotted for all possible test results to form the receiver operating characteristic curve. From this, likelihood ratios can be derived to calculate the probability with which a test result indicates the presence of the condition being sought. The diagnostic efficiency of different tests can be compared by their receiver operating characteristic curves, both quickly by eye, and formally by statistics. These points are illustrated by the comparison of serum urate and urinary calcium excretion in the assessment of pregnancy-induced hypertension. Receiver operating characteristic curves permit the rational comparison of investigations, and assist the selection of decision thresholds. They appear to have a useful place in the evaluation of diagnostic tests in obstetrics.

Transcervical resection of the endometrium (TCRE): elegy of the hysterectomy for menorrhagia? by A. Magos, R. Baumann & Sir A. Turnbull. Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Maternity Department, Headington, Oxford OX3 9DU

As an alternative to hysterectomy, 10 women complaining of menorrhagia were treated with hysteroscopic transcervical resection of the endometrium (TCRE) using an unmodified urological resectoscope. Six patients requested total resection of the endometrial lining with the intention of producing amenorrhoea, the remaining four preferring partial resection and hypomenorrhoea. Two women were found to have submucous fibroids at hysteroscopy which were resected along with the endometrium. There were no significant intra- or postoperative complications and nine of the women were discharged from hospital the day after surgery. Most were able to resume work and normal activities within 2–3 weeks. Follow-up over 3 months revealed significantly beneficial effects on the duration of menses, menstrual blood loss and menstrual pains in every case, as assessed by a daily prospective calendar, with half the women becoming amenorrhoeic after total resection. Hysteroscopy at 3 months showed intact uterine cavities in all but one, with fibrosis typically confined to the fundus, intrauterine adhesions in only one, and small areas of endometrium in the women who continued to menstruate. Simultaneous endo-uterine biopsy confirmed normal endometrial histology or showed evidence of an inflammatory response. Although these results are preliminary, TCRE may have an important role in the management of this common complaint.

Hypocalciuria and hypertension in pregnancy: a prospective study by M. C. M. Macintosh, A. C. T. Hutchesson*, S. L. B. Duncan & A. R. W.

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Significant hypocalciuria has been reported in women with pregnancy-induced hypertension (PIH) and elevated serum urate. This prospective study was designed to confirm the association and to clarify the timing of the reduction in calcium excretion to the onset of hypertension. Venous blood and 24-h urine samples were obtained serially from 138 selected women from the beginning of the third trimester of pregnancy. Weekly samples were taken if the woman was in hospital, but otherwise only when she attended the hospital clinic. Urate, albumin, calcium and creatinine were analysed in serum, and calcium and creatinine in urine. Of the 138 women, 124 were normotensive at 20 weeks. Of these, 40 women developed PIH, 20 of whom had proteinuria or elevated serum urate. The latter excreted less calcium (95% CI 1·64–4·07 mmol/24 h) than normotensive women (95% CI 4·40–5·61) ($P<0{\cdot}05$). In women who developed hypertension with renal changes a fall in calcium/creatinine ratio was closely related to the time of onset of hypertension. We conclude that a reduction in urinary calcium excretion may reflect the renal involvement of PIH.

The influence of pregnancy on cardiac haemodynamic responses to angiotensin II infusion by Ph. Loquet, F. Broughton Pipkin*, E. M. Symonds* & P. C. Rubin. Departments of Therapeutics and *Obstetrics, Nottingham University Hospital, Nottingham

In a previous study we reported the influence of pregnancy on blood flow in uterine and maternal carotid arteries. To assess the role of the heart in these changes, cardiac stroke distance and rising slope of the blood velocity waveform, and maximal blood velocity in the ascending part of the aortic arch were measured during infusion of increasing doses in eight non-pregnant and eight pregnant patients (mean gestational age 14 (SD 2) weeks). The measurements were performed using a pulsed Doppler ultrasound device (Doptek duplex centre, Doptek, Chichester) with a 2-MHz suprasternal transducer. The study groups were comparable for age, medical history, baseline blood pressures and smoking habits. Baseline pulse rate was significantly ($P=0{\cdot}025$) higher in the pregnant group (80 (SD 10) beats/min) than in the non-pregnant group (71(SD11) beats/min). Baseline maximal blood velocity was also significantly ($P=0{\cdot}001$) higher in the pregnant group (99 (SD 10) cm/s compared with 81·5 (SD 14) cm/s in the non-pregnant group). The stroke distance was slightly higher in the pregnant group (17 (SD 2) cm) than in the non-pregnant group (15·5 (SD 2) cm). The rising slope was not significantly higher in the pregnant group. This could reflect the fact that at this stage of pregnancy the heart is only starting to adapt morphologically (non-significant increase in stroke distance and rising slope) to an already changing vascular system (increased blood velocity). The increased pulse rate would be the first response to decreased peripheral resistance (reflected by increased blood velocities). In both groups, stroke distance, pulse rate, rising slope and maximal velocity decreased significantly ($P<0{\cdot}01$) from AII doses higher than 8 ng/kg/min in the non-pregnant group and 16 ng/kg/min in the pregnant group. The decreased vascular reactivity of the pregnant group is reflected in these changes. The slope of the association between diastolic blood pressure and maximal velocity is slightly steeper in the pregnant group, and a small extrapolation from the regression data shows that, even if the baseline maximal velocity were higher in the pregnant group, this advantage would be lost at a diastolic blood pressure of around 105 mmHg. This could mean that vascular adaptation to pregnancy precedes cardiac adaptation and that the protective effect of pregnancy seems to decrease when blood pressure increases.

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CORRESPONDENCE

Haemodynamic changes in gestational proteinuric hypertension: the effects of rapid volume expansion and vasodilator therapy

Dear Sir,
We read with interest the article by Belfort *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 634-641] on the haemodynamic changes that accompany volume expansion in pre-eclampsia, and the accompanying editorial by Duncan (1989).

Belfort *et al.* conclude that volume expansion may be of therapeutic benefit in the severely hypertensive patient with a low cardiac index. Similarly the accompanying editorial states that 'the notion of pharmacological vasodilatation of the arterial circulation and volume expansion is an appealing one, seeming to counter the effects if not the cause of the condition'.

Low plasma volumes and raised blood viscosity are consistently found in women with severe pre-eclampsia, and these changes may exert an unfavourable effect on placental perfusion. There may be no causal link but endogenous levels of aldosterone, the salt-retaining steroid, are also relatively low in this disease compared with normal pregnancy. For the last 9 months we have administered fludrocortisone, the synthetic mineralocorticoid, to selected patients with severe early pregnancy-induced hypertension, and several interesting observations have been made. The treatment appears to reduce peripheral oedema whilst raising plasma volume (in one case by 34%) with corresponding reductions in blood viscosity and haematocrit.

It is possible that the effects are not mediated purely through renal handling of sodium but that there is a direct effect on vascular permeability to sodium and water which could be relevant to the prevention of eclampsia (where cerebral oedema is a prominent feature).

When the optimum dose of fludrocortisone has been established, a placebo-controlled trial of this therapy is planned to determine whether this approach will be of any clinical benefit.

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Duncan S. (1989) Commentary Does volume expansion in pre-eclampsia help or hinder?*Br J Obstet Gynaecol* **96**, 631-633.

Gemeprost vaginal pessaries for inducing third-trimester intrauterine deaths

Dear Sir,
I read with interest the short communication by Shafi *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 745-746]. I have also used this prostaglandin analogue on five occasions for stillbirths at gestations ranging from 30 to 36 weeks. I would like to add a cautionary note. One patient was a 37-year-old woman who had had spontaneous vaginal deliveries at term in 1975 and 1977. At 35 weeks gestation during an uneventful third pregnancy she presented with an unexplained intrauterine death. The cervix was closed and posterior, so labour was induced using gemeprost vaginal pessaries; two pessaries were given 6 h apart. After the second pessary, contractions became regular and hypertonic. A fresh non-infected stillbirth was born 1 h 30 min later. The third stage was managed actively with delivery of a complete placenta after 5 min. There was no retroplacental clot. However, uterine bleeding began and she lost more than 2·5 litres. A coagulation screen 45 min after delivery revealed an acute disseminated intravascular coagulopathy

(DIC). The haemorrhage could not be controlled conservatively and an emergency hysterectomy was necessary. At operation there was no evidence of uterine trauma. An amniotic fluid embolus was suspected to have caused the acute DIC after the very short, hypertonic first stage of labour. Unfortunately no confirmatory tests were performed at the time. I note that in the small study by Shafi *et al.* the mean length of the active phase of the first stage was 1·65 h. Clinicians using gemeprost should be aware of the possible associated problems.

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Serum CA 125 in acute pelvic inflammatory disease

Dear Sir,

I read with great interest the article by Paavonen *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 574-579] reporting elevated serum CA 125 concentrations in acute pelvic inflammatory disease (PID). The authors describe a good correlation between CA 125 levels and the severity of inflammation.

However, no explanation on the possible cause of elevated CA 125 values during PID is given. Augmented expression of several tumour-associated antigens under the influence of human leukocyte interferon was demonstrated by Greiner (1986). Recently, significant interferon-gamma levels were reported in 60·4% of women with PID (Grifo *et al.* 1989). Thus, it seems conceivable that elevations of the tumour antigen CA 125 described by Paavonen *et al.* simply result from an endogenous production of interferon, which leads to an enhanced CA 125 expression.

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Diagnostic role of dilatation and curettage in the management of abnormal premenopausal bleeding

Dear Sir,

Hammond *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 496-497] mentioned that among their 356 premenopausal patients who had dilatation and curettage, abnormal endometrial histology was found only in those over 40 years of age. The number of patients below 40 years of age was not mentioned.

We had a different experience. Amongst the 471 premenopausal patients who underwent dilatation and curettage in our hospital in 1988 because of menstrual problems, 11 had abnormal histology. One of them who was 33 years of age had adenocarcinoma of the endocervix diagnosed by dilatation and curettage, the other 10 had endometrial pathologies. Eight women had cystic glandular hyperplasias (four were <40 years of age), one (aged 33 years) had adenomatous hyperplasia and one (aged 56 years) had endometrial carcinoma. Of the 471 women investigated 219 were <40 years of age, and of the 11 patients with abnormal histology, six were <40 years of age. Thus dilatation and curettage continues to remain a good diagnostic tool for young patients who present with abnormal premenopausal bleeding in our population.

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Commentary. Human immunodeficiency virus infection in women

Dear Sir,

In response to your commentary 'HIV infection in women' by Johnson & Webster [*Br J Obstet Gynaecol* (1989) **96**, 129–134], there are certain additional points to be made, and areas that require clarification.

The authors have not referred to the apparent increase in cervical intraepithelial neoplasia described by several groups in HIV-positive women (Bradbeer 1987; Spurret *et al.* 1988). The implications of this are still being assessed by controlled trials, but it is our current practice to offer cervical cytological screening and, preferably, colposcopic examination of the lower genital tract to our HIV-infected women every 6 months.

The authors omit to discuss many of the issues involved in the 'antenatal screening' debate, concentrating mainly on the epidemiological benefits of such a scheme. Any identification screening which does take place should be for the benefit of the patient and not only to gain epidemiological information. Many units are extremely concerned about the risk to health care workers who operate on and deliver these women. Recent work has highlighted for instance the high incidence of glove puncture (54%) incurred by the surgeon at caesarean section. The importance, even in the presence of a screening programme, of introducing a 'one-tier infection control policy' protecting staff in all circumstances needs to be addressed. This system has the benefit of protecting staff from patients with a false-negative HIV antibody test, and those with other infectious diseases such as hepatitis B. Instituting an antenatal screening programme may frighten those who require the help most, drug addicts, immigrants, and those with poor social circumstances, from attending for antenatal care. Finally, we feel that the authors have adopted a rather naive approach to the question of pregnancy in HIV-infected women. Despite counselling, many patients are still determined to become pregnant, and in that case they might be encouraged to become pregnant as soon as possible in the early stages of the disease when they are relatively well and the risk of vertical transmission may be smaller. The situation needs to be approached with sympathy and tact rather than condemnation, and more accurate information in this area is urgently required. Others become pregnant accidentally but feel they cannot consider a termination.

This underlies the importance of good family planning advice encouraging patients to use reliable methods such as the contraceptive pill or, failing that, to consider other methods. Barrier methods should be encouraged to reduce the spread of HIV and other sexually transmitted diseases.

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Authors' reply

Dear Sir,

We thank Dr Smith and colleagues for their comments. It is true that there are case reports indicating an excess of cervical pathology in women with HIV and AIDS. This is logical and is the experience at the Royal Free Hospital but we purposefully tried to confine our comments and references to proper controlled studies rather than add to the misguided mythology on the subject by premature conclusions. We await with interest the outcome of the twice-yearly colposcopic study referred to but wonder what advantage this has over cytological screening. It may help oncologists to obtain new colposcopes out of HIV funding but it may have little effect on prognosis.

After some partial sympathy with the authors' first paragraph there is much disagreement in the rest of the letter. The antenatal screening debate remains controversial but there are two issues. First, as discussed in our article, testing and counselling in the antenatal clinic should always be available for women who request it and should be offered to those with risk factors. We accept that epidemiological information is essential for health planning but this is a second issue which we have discussed at length elsewhere (Johnson & Griffiths 1989).

We cannot agree that screening has a proven place in the reduction of occupational exposure. There is no evidence in the literature to suggest that needle stick injuries are less common if the HIV status of the patient is known. The significance of the apparent high incidence of glove puncture quoted by Dr Smith *et al.* is not clear. If it is true that 'many units are extremely concerned about the risk to health care workers' then this must reflect irrational anxiety on the part of those staff. Provided that the simple measures appropriate for the control of hepatitis B were introduced into such units as recommended 10–15 years ago there should be no need for additional precautions for the control of HIV.

Our most severe objection is the suggestion that we have a naive approach to the question of pregnancy in HIV infection. Our critics suggest that patients keen to become pregnant might be encouraged to do so as early as possible in their disease course. Would they give the same advice to women with rubella infection? To what length do obstetricians go to ensure a precise prenatal diagnosis of conditions a fraction as lethal or disabling as paediatric HIV infection?

We are not recommending anything as draconian as compulsory sterilization and abortion but we must recognize that the legacy of pregnancy in women infected with HIV is an orphaned child with a risk in excess of 25% of being infected. All of these children will probably die. We do not need to be reminded that these patients need to be treated with sympathy and tact but we would remind Dr Smith and his colleagues that the job of the medical adviser is to explain frankly all of the information available about HIV in pregnancy and then support the patient's own decision.

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Minimal/mild endometriosis and infertility

Dear Sir,

We read the review article by Bancroft *et al.* [*Br J Obstet Gynaecol* (1989) **96,** 454–460] with great interest. The authors postulate, like many before them, a causal association between mild endometriosis and subfertility. However, it would appear that the literature lacks strong evidence to support this contention. Undoubtedly a high prevalence of endometriosis in the infertile women (reports vary from 6 to 50% (Kistner 1979; Musich & Behrman 1982; Hull *et al.* 1985; Glass 1986)) and a low prevalence in fertile women (2% reported by Strathy *et al.* (1982)) do suggest a strong association, but this is not the same as the suggestion that endometriosis is causal.

Recently we hypothesized that if endometriosis was indeed the underlying cause of infertility, then it should be less common among women whose partners were apparently subfertile. We reviewed the laparoscopy reports of 292 women with primary infertility (Mahmood & Templeton 1989). The partners of 171 (58%) had normal semen by WHO criteria (WHO 1980) while the partners of 121 (42%) had subfertile semen. Both groups were comparable for duration of infertility and age at laparoscopy. The prevalence of mild endometriosis (stage I–II; revised AFS<15) was in fact lower among women whose partners had normal semen (12 *vs* 20%, $P<0{\cdot}01$). Interestingly, moderate to severe endometriosis (stage III–IV; revised AFS>16) was more prevalent in women whose partners had normal semen than in those whose partners had abnormal semen (14 *vs* 5%, $P < 0{\cdot}05$).

Thus we noted a high prevalence of moderate/

severe endometriosis in patients whose partners had normal semen, and a higher prevalence of mild endometriosis in women whose continuing infertility could be mainly attributed to defective spermatogenesis. These findings provide some evidence that mild endometriosis may not be the primary cause of infertility in all the women, and that it is possible that infertility for other reasons may predispose to or exacerbate the tendency to develop endometriosis in susceptible women.

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Authors' reply

Dear Sir,
We would like to thank Mr Mahmood and Professor Templeton for their interest in our paper. However, in contrast to their suggestion that we postulate a causal association between mild endometriosis and infertility, the reverse is true.

Literature relating to the significance of minimal/mild endometriosis in infertility is summarized briefly in the opening part of the paper, which suggests 'that endometriosis of a minimal or mild degree may be an incidental finding and of no importance in the pathogenesis of infertility'.

Whilst accepting that the causality of the association between minimal/mild endometriosis and infertility remains a matter for debate, the paper goes on to explore some of the recent literature relating to this association. Finally, the paper concludes that 'The multiplicity of these abnormalities [those associated with minimal/mild endometriosis and infertility] suggests that the development of endometriosis may be a common consequence of these, rather than their cause, and as such, treatment of the disease will not necessarily improve fertility'.

Having reiterated the conclusions gleaned from reviewing the extensive literature in this area, it was of interest to note that Mr Mahmood and Professor Templeton's own work added further evidence to support our conclusion.

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Serum CA 125 in acute pelvic inflammatory disease

Dear Sir,
We read the article on serum CA 125 in acute pelvic inflammatory disease by Paavonen *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 574–579] with interest, but feel that several points need to be considered.

In the literature, CA 125 is expressed in units/ml (Bast *et al.* 1983). In the paper by Paavonen *et al.* (1989) they expressed CA 125 in μg/l. It would be helpful if the conversion factor were given so that this paper could be compared with other work on CA 125.

Secondly, the upper limit of serum CA 125 is usually taken as 35 units/ml (Bast *et al.* 1983; Halila *et al.* 1986), or occasionally as 65 units/ml (Niloff *et al.* 1984). Why did the authors take 30 μg/l as their upper limit of normal?

Thirdly, the choice of their group of normals needs further clarification. It has been reported that menstruation and early pregnancy are both associated with a significant rise in serum CA 125 (Pittaway & Feyez 1987; Mastropaolo *et al.* 1986; Jacobs *et al.* 1988). Was this taken into consideration? Finally the age range of these normal women was 25–75 years with a mean of 55 years. Haga *et al.* (1986) have shown that women under 49 years of age tend to have higher serum CA 125 than those over 49 years of age, and have suggested that separate reference levels should be set.

If these points had been considered the results of Paavonen *et al.* might have been different.

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Authors' reply

Dear Sir,

We thank Drs Irvine and Shaw for their comments. They are right; CA 125 was expressed in units/ml (as is correctly shown in Figs 1 and 2). Unfortunately there was a typing error in the text. All CA 125 units should have been units/ml and not µg/l. We selected 30 units/ml as a cut-off level simply according to the manufacturer's recommendations (CIS International). We certainly are aware of studies suggesting that serum CA 125 levels increase during menstruation and early pregnancy, but neither this nor small differences in the cut-off level change the most important observation of our study, i.e. a dose-response type of effect inflammation seems to have on serum CA 125 levels. In an ongoing study (Aaran *et al.* 1989) we are finding significant elevations in serum CA 125 also among outpatients with proven PID suggesting that CA 125 might be a more sensitive marker for inflammation than any acute-phase proteins such as CRP.

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BOOK REVIEWS

Advances in Reproductive and Perinatal Medicine edited by W. C. Cheng & S. L. Tan. P.G. Publishers, Singapore, no price given, obtainable only in Singapore

The origin of this book was a seminar convened at the Thomson Medical Centre in Singapore at the time of the 12th World Congress of Fertility and Sterility in 1986. The majority of the contributors are from Singapore or the UK. A variety of topics are addressed, including investigation and treatment of amenorrhoea, assessment of male infertility, treatment with pulsatile LHRH and LHRH analogues, the role of IVF in the treatment of infertility, hormonal contraception, prenatal diagnosis and genetic counselling. Most of the chapters are authoritative updates on the various topics and are well referenced. They provide useful reading for those who wish to ensure that their knowledge of any of the particular subjects is up to date, but as all these are rapidly developing fields the reviews will not be up to date for very long. The fact that the book is obtainable only in Singapore is likely to limit the readership.

Gillian Lachelin

AIDS and Obstetrics and Gynaecology (Proceedings of the 19th Study Group of the Royal College of Obstetricians and Gynaecologists) edited by C. N. Hudson & S. Sharp. Springer-Verlag, London, 1988, 352 pages with figures and tables, £57.80

These proceedings, first published in November 1988 by the Royal College, are now generally available in their original form but under new cover. The 19th Study Group met in March 1988 to discuss the impact of HIV infection on midwifery, obstetrics and gynaecology. New data are published regularly in the journals, but this volume, covering the situation as of early 1988, has not yet become passé. The format is standard for such proceedings, with 32 papers and intermingled edited discussions.

The first half of the volume deals with what should be our prime concerns—the care and counselling of pregnant women (or 'clients' as they are apparently widely known!). There are many excellent contributions on the virology, epidemiology and natural history of the infection in pregnancy and infant life. It seems the prevalence is still low, but not accurately known without large-scale surveys. The risk of vertical (materno-fetal) transmission is in the order of 25%, but various reasons are given why women might not seek termination of pregnancy on these grounds alone. Pregnancy does not appear to have a major adverse effect on previously asymptomatic HIV infection, contrary to what we believed 3 years ago. Controversies about antenatal testing are discussed, and the paper on ethical considerations is well balanced. The view is predominant that universal attributable (named sample) testing without consent was to be eschewed.

After this very purposeful beginning the book becomes a little aimless, but there are excellent reviews on HIV-infected health care workers, HIV and blood transfusion (of largely historical interest), and AIDS and human milk banking. Occupational infection is so rare that recommendations on staff protection are based largely on conjecture. No agreement is reached about whether we should assiduously try to identify high-risk women and apply rigorous staff safety measures in those cases only, or whether we should adopt a set of measures more acceptable to staff and patients, applying them in all cases, regardless of HIV status (identification of which becomes unnecessary as far as the immediate care of the mother is concerned). This latter, 'one-tier' approach is recommended for neonatal care. Readers may be disappointed in the (understandable) lack of consensus and firm advice. Widespread prejudices will have to be overcome even among medical and nursing staff, who 'want all women screened' (p. 252). Testing must be of potential benefit to the patient.

The reissue of this very important work might have been an opportunity to correct a few minor faults, such as the apparent balanced translocation of the discussions on pages 261 and 289, and the absence of the paper on methods of antenatal diagnosis. A whole page of print was absent in my review copy. Nevertheless, this must be the definitive UK text on this subject, and it ought to be available on all maternity units. Individual fellows and members who have bought the College's edition, at one-third the cost, are doubly fortunate.

Paddy Forbes

Ultrasonography in Obstetrics and Gynecology Second edition edited by Peter Callen. W. B. Saunders Company, Philadelphia, London, 1988, 496 pages with figures and tables, £40.00

Obstetric ultrasound has matured to a stage at which the rate of innovation seen in the past two decades is unlikely to be repeated in the future. The main emphases now should be on reflection and consolidation, and a firm commitment to training so ensuring that the best standards of practice are made universal. Books about obstetric ultrasound are also maturing and this volume edited by Peter W. Callen has now reached its second edition. A good book it is too—substantially better than the first edition. Both obstetric and gynaecological applications of ultrasound are included, as is, incongruously, a chapter on magnetic resonance imaging. Inevitably in such a large book (almost 500 pages), one can take issue with some statements by some writers but this does not detract from what is overall a considered and authoritative text. It is inevitable also in a multi-author book that some sections are better than others and that the balance is not perfect throughout, thus the chapter on hydrops fetalis is almost twice the length of a rather poor chapter on fetal growth. The quality of the illustrations is almost invariably good; these are nearly all of the white-on-black format but there are a few ugly exceptions.

This book is of good financial and educational value and it is highly recommended. It is probably the best available text at the moment for reference by the obstetrics and gynaecology ultrasonographer who has passed the novice stage.

J. Neilson

Contemporary Obstetrics and Gynaecology edited by Geoffrey Chamberlain. Butterworths, London, 1988, 434 pages with figures and tables, £27.50

It is sad to see that this is the last volume of *Contemporary Obstetrics and Gynaecology* but the editor and Butterworths are to be congratulated on plunging into the 'new journal' melée. Their aim, to produce the results of research work for general assimilation without the inevitable delays inbuilt in the publication and printing of a book, is to be applauded, and the new review journal of the same name as this book is to be wished every success. The *Contemporary Obstetrics and Gynaecology* series has indeed brought to a wider audience research work that might otherwise have escaped notice or aroused passing interest, and the delay in publication has meant renewed interest in some topics. This book contains a pot-pourri blended at the editor's whim: a chiaroscuro of fascinating chapters, with obstetric topics outweighing gynaecology by 116 pages and somehow 'Viral infection in pregnancy' appearing in the gynaecology section!

Part 1, Obstetrics, contains chapters dealing with topics of current concern, highlighting recent research in a variety of fields confirming the editor's admission that the choice of subjects is idiosyncratic. The illustrations have reproduced well, particularly the children in Chapter 5 and the MRI pictures in Chapter 9. The graphs and charts are clear too but it is the list of references that the obstetrician/gynaecologist in training will find especially useful.

Part 2, Gynaecology, includes chapters dealing with major controversies. For example, Chapter 25 discusses prophylactic oophorectomy. The cervix figures prominently from Chapter 16 'Collagen changes' through Chapter 21 'Screening', Chapter 22 'HPV and CIN' and Chapter 23 'What to do with CIN'. These sections will provide particular interest and supplement standard texts.

The divergent, original and challenging ideas put forward in many of these chapters will be a great stimulus to practising obstetricians and gynaecologists, but those in training must beware of quoting blindly, particularly under examination conditions.

Gillian M. Turner

Effective Prevention of Preterm Birth: the French Experience Measured at Haguenau Birth Defects Original Article Series Vol. 25 No. 1 edited by E. Papiernik, L. G. Keith, J. Bouyer, J. Dreyfus & P. Lazar. March of Dimes Birth Defects Foundation, White Plains, New York, 1989, 234 pages, $25.00

'A growing awareness of perinatal problems developed in France during the late 1960s. The focus of this process was the need to deal with handicaps of perinatal origin'. Thus begins Emile Papiernik's introduction to this English language edition of the report of trends in perinatal practice and the outcome of pregnancy observed at the maternity hospital in the Alsatian town of Haguenau between 1971 and 1982. There is fairly strong evidence that the rate of preterm birth declined not only in Haguenau, but in France more generally during the 1970s. Whatever the factors responsible for this trend, it would be perverse not to regard it as welcome. However, as Philippe Lazar notes in his important 'methodological reflections' on the Haguenau study, it is not possible to reach confident conclusions about the reasons for the decline in the rate of preterm birth. He notes the daunting difficulties facing any researcher who wishes to unravel the relative importance of the social, economic and medical policies adopted in France in the context of a concerted national attempt to tackle the problem. The breadth of this French approach to the prevention of preterm birth owes a great deal to the personal influence of Emile Papiernik: there are few obstetricians whose research into possible ways of preventing preterm birth ranges from studies of hormonal and surgical approaches, to the investigation of the effects of modifications of work patterns. So this book contains important French lessons which are well worth learning. If I have a criticism it is that, like most texts in which there is reference to 'handicaps of perinatal origin', there is no discussion of what these handicaps are (or might be), let alone any data showing whether the programme (in Haguenau or in France more generally) has achieved its main objective of preventing them. The fact that the book has been published by the March of Dimes Birth Defects Foundation can only help to reinforce a common belief, which remains unsupported by good evidence, that reduction in preterm birth will be reflected in reduced rates of 'handicaps of perinatal origin'. This belief may prove to be justified; but it is time to stop reiterating it and to start testing its validity with actual data, not logical reasoning. It should be a cause for concern that the birth cohort prevalence of cerebral palsy in Sweden (which has one of the lowest recorded rates of preterm birth) has been rising inexorably since the late 1960s, and is now higher than at any time since records began.

Iain Chalmers

Books received some of which may be reviewed at a later date

Diabetic Pregnancy (Volume 13 in the series *Current Reviews in Obstetrics and Gynaecology*) edited by M. Brundenell & M. C. Doddridge. Churchill Livingstone, Edinburgh, London, 1989, 160 pages illustrated, £19.50

Surgical Management of Soft Tissue Sarcoma by Man H. Shiu & Murray F. Brennan. Lea & Febiger, Philadelphia, London, 1989, 297 pages fully illustrated, £42.54

Smith's Recognizable Patterns of Human Deformation Second edition by John M. Graham Jr. W. B. Saunders Co., Philadelphia, London, 1989, 183 pages fully illustrated, £23.50

Electronic Fetal Heart Rate Monitoring: A Practical Guide by Paul L. Wood & H. Gorden Dobbie. Macmillan Press, London, 1989, 86 pages with figures and tables, hardback £18.95, softback £8.95

The Year Book of Obstetrics and Gynecology 1989 edited by Daniel R. Mishell Jr, Thomas H. Kirschbaum & C. Paul Morrow. Year Book Medical Publishers, Inc., Chicago, London, Boca Raton, 1989, 505 pages with figures and tables, £40.00

Preparation and Advice for the MRCOG by V. R. Tindall, R. H. Martin & R. W. Burslem. Churchill Livingstone, Edinburgh, 1989, 256 pages illustrated, £9.95

Government Policy and Women's Health Care: The Swedish Alternative by Gunnela Westlander & Jeanne Mager Stellman. Haworth Press, New York, London, 1988, 180 pages with figures and tables, £34.95

Doctors' Decisions: Ethical Conflicts in Medical Practice edited by G. R. Dunstan & E. A. Shinebourne. Oxford University Press, Oxford, 1989, 248 pages, £22.50

Fetal Monitoring. Physiology and Techniques of Antenatal and Intrapartum Assessment edited by John A. D. Spencer. Castle House Publications, Tunbridge Wells, 1989, 248 pages with figures and tables, £35.00

Update on Hormonal Treatment in the Menopause (Volume 13 in the series *Progress in Reproductive Biology and Medicine*) edited by M. L'Hermite. Karger, Basel, 1989, 108 pages with figures and tables, Sw.Fr.98, DM 117, £40.90, US $65.00

Human Sexuality and its Problems Second edition by John Bancroft. Churchill Livingstone, Edinburgh, 1989, 748 pages fully illustrated, £24.95

Brain Opioid Systems in Reproduction edited by R. G. Dyer & R. J. Bicknell. Oxford University Press, 1989, 365 pages with figures and tables, £45.00

Human Papillomavirus and Cervical Cancer (World Health Organization International Agency for Research on Cancer. IARC Scientific Publication No.94) edited by N. Munoz, F. X. Bosch & M. Jensen. Oxford University Press, 1989, 155 pages with colour plates, £19.00

A Pocketbook of Obstetrics and Gynecology edited by N. O. Sjöberg & B. Åstedt. Parthenon Publishing, Carnforth, Lancs, 1989, 204 pages, £12.95

Williams Obstetrics: A Study Guide Second edition by Thomas M. Julian. Prentice-Hall International, Inc., Hemel Hempstead, 1989, 319 pages, £12.95

Study Guide for Obstetrics. Normal and Problem Pregnancies by Steven G. Gabbe, Jennifer R. Niebyl & Joe Leigh Simpson. Churchill Livingstone, New York, Edinburgh, 1989, 160 pages, £16.50

ABC of Clinical Genetics by Helen Kingston. *British Medical Journal,* London, 62 pages fully illustrated, UK £10.95, abroad £13 including air postage

World Health Statistics Quarterly Volume 42, No.2, 1989 Travel Medicine World Health Organization, Geneva, FR 23.00

Regaining Bladder Control Second edition by Eileen Montgomery. Clinical Press, Bristol, 1989, 28 pages, £2.50

Recent Advances in the Management of Infertility edited by Christopher Chen, S. L. Tan & W. C. Cheng. McGraw-Hill Book Co., Singapore, 371 pages with figures and tables, $47.95

Oxford Handbook of Clinical Specialties Second edition by J. A. B. Collier & J. M. Longmore. Oxford University Press, 1989, 787 pages, £10.95

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COMMENTARIES

The benefits of combined oral contraceptives

Like all drugs, combined oral contraceptives (COCs) have side-effects that may be harmful or beneficial. During the last 20 years their adverse effects have been fully reported (Shaw 1987) but their benefits have been almost ignored. This has given the profession and the public a lopsided view of their safety. In 1985 a Gallup poll sponsored by the American College of Obstetricians and Gynecologists found that three-quarters of women thought there were substantial risks with the pill, one-third thought the pill caused cancer and only a minority thought it was less dangerous than childbearing. A survey of middle-class women in developing countries confirmed that the beneficial effects of COCs are virtually unknown (Grubb 1987).

The benefits of COCs range from preventing cancer to treating dysmenorrhoea (Connell 1987; Fraser 1986; Kubba 1985) but the most obvious is effective prevention of pregnancy. The failure rate of COCs is 1–3 per 100 woman-years (Grimes 1986; Guillebaud 1985), which compares favourably with all other contraceptives except injectable progestogens and sterilization. Pregnancy carries an overall maternal mortality ranging from 1 in 10 000 in developed countries to 1 in 150 in Africa (WHO 1987). The excess mortality associated with earlier COCs (almost entirely due to cardiovascular complications) was 1 in 10 000 per year for smokers under the age of 35 and less than 1 in 50 000 for non-smokers under 35 (Kay 1984*b*; Pepperell 1986). Cardiovascular risks may be lower with modern low-oestrogen pills (Vessey *et al* 1984). In 1981 in Massachusetts there was one pregnancy-related death per 100 000 women under 35 but no contraceptive-related deaths among non-smokers in the same age group (Sachs *et al* 1984).

It has been estimated that the risk of ectopic pregnancy in COC users is as low as 10% of the risk faced by women who use no contraception. In the Oxford–Family Planning Association (FPA) cohort study, none of the unplanned pregnancies in COC users was ectopic, compared with 6·9% of pregnancies among users of intrauterine contraceptive devices and 0·6% among women using other methods or none (Kols *et al.* 1982).

When the relation between COCs and malignant disease is considered, attention has tended to focus on breast and cervical cancer The effect of COCs on the risk of breast cancer is still unclear (Drife 1989; Leading Article 1989; Shaw 1987) but COC users may have an increased risk of cervical neoplasia (Beral *et al.* 1988) and should have regular smears (Shaw 1987).

At least 12 studies have concluded that the COC protects women from ovarian cancer. In a recent report, women who had used COCs had a relative risk of epithelial ovarian cancer of 0·6 compared with women who had never used them: the protective effect (which is independent of COC formulation) was seen in women who had used COCs for as little as 3–6 months and it continued for 15 years after use ended (Cancer and Steroid Hormone Study 1987*a*). The biological basis of this protection is unclear but it may be due to the suppression of ovulation (Khoo 1986).

Twelve studies have investigated the relation between COCs and endometrial cancer, and 10 have noted a decreased risk. In the USA the Cancer and Steroid Hormone Study concluded that women who had used COCs for at least 12 months had an age-adjusted relative risk of endometrial cancer of 0·6 relative to those who had never used COCs. The protective effect persisted for at least 15 years after COC use ceased, was independent of formulation and protected against adenocarcinoma, adenoacanthoma and adenosquamous carcinoma (Cancer and Steroid Hormone Study 1987*b*). The WHO Collaborative Study (1988), which involved 11 participating centres throughout the world, concluded that the relative risk of endometrial cancer among COC users was 0·55, and the protective effect was seen in areas of high and low incidence.

Numerous studies have shown that COCs reduce the risk of benign breast disease (Livolsi *et al.* 1979). This protective effect applies to both fibrocystic disease and fibroadenoma, and is seen after 2–4 years of COC use. Benign breast disease is a risk factor for breast cancer, so it is disappointing that COCs do not cause a similar reduction in the risk of breast cancer. This paradox may be due to COCs protecting against some types of benign breast disease but not others. A study of the degree of atypia in fibrocystic disease showed that women with a high degree of atypia had similar patterns of COC use as was noted in control subjects, whereas women with low and intermediate degree of atypia had less COC use (Pastides *et al.* 1983). In other words, COCs protect against the types of benign breast disease that are not associated with breast cancer.

Because COCs suppress the ovaries they reduce the occurrence of functional ovarian cysts. It has been estimated that the annual incidence of functional cysts that necessitate admission to hospital is 38/100 000 non-users but only 3/100 000 COC users (Mishell 1982). The Oxford–Family Planning Association (FPA) study confirmed that functional cysts of the ovary occurred much less frequently in women who had taken COCs within the previous 6 months. Corpus luteum cysts were reduced by 78% and follicular cysts by 49% (Vessey *et al.* 1987). About 28 operations for functional ovarian cysts are avoided per 100 000 COC users every year. Progestogen-only pills do not have a protective effect, and COCs do not protect against benign teratoma or cystadenoma (Vessey *et al.* 1987).

The Royal College of General Practitioners' (RCGP) cohort study showed that fibroids were less commonly diagnosed among COC users (Kay 1984*a*). Initial results from the Oxford–FPA study did not confirm this. but a more recent case-control study based on women recruited to the Oxford–FPA study concluded that the risk of fibroids decreased consistently with increasing duration of COC use: there was a roughly 17% reduction in risk with each 5 years of pill use, and the risk was reduced by about 30% in women who had used COCs for 10 years (Ross *et al.* 1986).

COCs reduce the risk of pelvic inflammatory disease by about 50% (Grimes 1986; Higgins *et al.* 1985), partly because cervical mucus becomes thicker and less penetrable by bacteria, and possibly because of direct inhibition of the growth of gonococci in the fallopian tubes (Kols *et al.* 1982). The protective effect disappears soon after the pill is stopped. It has been suggested that protection applies to chlamydial as well as to gonococcal infection (Grimes 1986) but 12 of the 14 relevant studies have shown a two- to threefold increase in cervical chlamydial infection among COC users (Washington *et al.* 1985). Among university students, the prevalence of endocervical chlamydial infection was lower in women using intrauterine or barrier contraception than in those using COCs or no contraception (Harrison *et al.* 1985), but this may reflect sexual activity rather than a direct effect of COCs (Gall 1986). COCs may protect against chlamydial perihepatitis (Wolner-Hanssen 1986), and so although the risk of cervical chlamydial infection is related to sexual activity, COCs may protect the upper genital tract and peritoneum. However, in a series of women with infertility due to tubal adhesions, Cramer *et al.* (1987) failed to demonstrate any protective effect of previous COC use.

According to the RCGP study, COCs halve the prevalence of menorrhagia, intermenstrual bleeding and irregular periods (Mishell 1982) but modern low-dose pills may involve a higher prevalence of breakthrough bleeding (Shearman 1986). COCs reduce the amount of menstrual loss. The RCGP study showed a 50% reduction in the frequency of iron-deficiency anaemia, and a 40% reduction in the frequency of dysmenorrhoea, and premenstrual tension was less common although the extent of the reduction is uncertain because this symptom is difficult to quantify.

The use of COCs does not worsen seizures in women with epilepsy but may improve seizure control in women with 'menstrual' or 'catamenial' epilepsy. A protective effect against thyroid disease has been reported (Frank & Kay 1978). COCs have no effect on the risk of mental disorders (Vessey *et al.* 1985), and do not affect the prevalence of thrush (Davidson & Oates 1985; Loudon *et al.* 1986).

The RCGP study showed a 50% reduction in the occurrence of rheumatoid arthritis in COC users, and a retrospective case-control study in the Netherlands showed a similar decrease, but more recent studies in the United States and in

Sweden have failed to show a protective effect (del Junco *et al.* 1985). It has been suggested that the more recent, negative study was least affected by bias (Esdaile & Horwitz 1986), but the question is still debated (Spector & Silman 1987).

Today the steroid content of 1 month's supply of the COC is about the same as that contained in one pill 25 years ago (Sapire 1988). Most of the benefits of COCs appear to derive from suppression of ovulation and are likely to be unchanged by the reduction in the steroid content. In contrast, the adverse effects—such as the cardiovascular risks—are more likely to be dose related. It seems likely that the reduction in dosage, together with the exclusion of 'high-risk women', has reduced the risks associated with COCs (Porter *et al.* 1987) but not the benefits.

It is at last being recognized that prescribers and manufacturers can do more to make women aware of the benefits of oral contraceptives, and the United States Food and Drug Administration has recommended that pill packages should in future describe the benefits of COCs (Kubba 1985). It would be naïve to hope that the media will give the same prominence to the benefits of the pill as to its adverse effects, but as the public becomes accustomed to 'scare' headlines on this subject, women will rely more on their doctors to provide balanced and objective information. It is important that general practitioners and specialists remind themselves from time to time about the benefits that are too easily overlooked or taken for granted.

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Posture in labour

Most midwives and obstetricians are asked at some time to give an opinion regarding the posture best suited for a woman in labour. The tradition during this century has been for women to be delivered lying in bed either in the dorsal or the lateral position. There are occasions, however, when other postures may be preferred, either for medical reasons or because the woman or her attendants wish to follow current vogue.

There has been considerable pressure from certain groups of childbirth educators to encourage the medical and midwifery professions to allow far more flexibility in the management of labour including the range of delivery positions offered. They have suggested that postures other than the conventional ones used by the majority of midwives are beneficial to the parturient (McKay 1984)

The increasing interest in alternative delivery positions over the last 20 years has not been ignored by producers of medical equipment. Birthing chairs have been developed and delivery beds redesigned to facilitate the use of various postures for birth. In the past it was maintained that one of the advantages of a woman lying in bed during her labour was that it facilitated fetal monitoring. The manufacturers of electronic monitoring equipment quickly overcame this potential problem by developing radiotelemetry systems enabling fetal monitoring to be performed while the woman was fully ambulant.

So much past obstetric practice has been based on anecdotal rather than scientific evidence that it is not surprising that equipment such as radiotelemetry and birth chairs has been introduced to labour wards without adequate assessment. Its use should not be regarded as a passport to success, guaranteeing either a good outcome or a good 'experience'. It is essential that accurate information should be available both to guide obstetricians on the value of such expensive equipment and also, perhaps more importantly, to advise pregnant women about the risks and benefits of any approach they wish to make to the management of their labour, including the use of alternative delivery positions.

Fifteen years ago the first comparative studies were carried out to attempt to assess the benefits of ambulation during the first stage of labour. The study designs varied greatly and the conclusions differed considerably. They can be roughly divided into those which showed a benefit from ambulation (Liu 1974) and those which did not (McManus & Calder 1978). It is an inherent problem when recruiting women to randomized studies that most participants will have a preferred choice before entering the study. If all patients are randomized many will not keep to their group allocation (Williams *et al.* 1980) and, if recruitment is limited to those women who are interested in the subject under study, the women allocated to the new treatment will tend to be more satisfied than those that are allocated to conventional management (Flynn *et al.* 1978). This may then affect the outcome. Such problems may be the reason why the results of these studies have been inconsistent.

It has been suggested recently (McNabb 1989) that there are too many 'physiological and emotional' variables associated with labour to make the results of a randomized study in this field of obstetrics meaningful.

A prospective observational study by Stewart & Calder (1984) approached the problem from a different angle. They attempted to assess whether or not the woman's choice of posture during the first stage of labour had any correlation with its outcome. The results of this study showed that those women who chose to be and remained ambulant for most of their labour tended to have shorter labours and require less analgesia when compared to those who chose to remain in bed. This could suggest that ambulation was beneficial. A third group of women, however, who initially chose to be ambulant then took to their beds early in labour had poorer outcomes than the other two groups. This would not be expected if ambulation itself was beneficial. The possible interpretation of these findings was that it was short, 'easy' labours which permitted ambulation rather than ambulation producing 'easy' labours. The study did, however, suggest that although there was no apparent benefit, there was no reason to prevent high-risk women from being ambulant as radiotelemetry was an effective form of continuously monitoring their labour. Such observational studies produce interesting information but because of their uncontrolled design no firm conclusion can be drawn about the risks and benefits of any specific variable being studied.

There is little doubt that the recumbent dorsal position is disadvantageous to labour outcome but, apart from this, the available evidence suggests that it is unlikely that any one position is particularly advantageous. The work of Roberts *et al.* (1983) may well be important. They suggested that changes of posture rather than the posture itself were the important factor in improving uterine activity in the first stage of labour

Studies carried out to investigate the effect of position in the second stage of labour are easier to interpret. Most have used specially manufactured birth chairs and compared the sitting position to the more conventional 'propped' dorsal position. This has the advantage of standardizing the posture adopted by women in the study group (Turner *et al.* 1986; Stewart & Spiby 1989). They have not produced conclusive results regarding certain outcomes, such as the need for instrumental delivery and the degree of perineal trauma. This may be due more to the variation in midwifery and obstetric practice between units than to a direct relation to the posture adopted. However, there have been two consistent findings: delivery using a birth chair does not reduce the duration of the second stage and is associated with a greater blood loss at delivery. At present it is prudent to advise women who request a birth chair that although they may feel more comfortable, the efficiency of labour is not improved, and there may be some added risk.

It is possible that the sitting position adopted in the birth chair is too close to that of the 'propped' dorsal position to enable a significant difference to be found in some outcomes. A comparison between conventional management and the more 'natural' positions advocated by some workers (e.g. squatting and knee/elbow) may identify other differences. The trial described by Gardosi *et al.* in this issue of the Journal (p. 1290) is therefore of considerable interest. It does, however, exemplify the numerous difficulties facing investigators who attempt to study this area of pregnancy. The authors deliberately avoided standardizing posture in the second stage in women allocated to 'upright' positions, in order to overcome the fixed sitting position imposed by birth chairs. As they have included women adopting several different postures their findings are a little difficult to interpret. The 'upright' group as a whole did better than the 'recumbent' group but the study design does not allow differentiation between the postures that were most beneficial and those that may possibly have been detrimental. Midwife and patient bias is also apparent, a problem that has been encountered by other workers in the past. It is interesting that the actual delivery position which was determined by the midwife, presumably in consultation with her patient, was similar in both upright and recumbent groups. Midwifery practice and patient expectation provide powerful resistance to change.

This study, which was considered by the authors to be exploratory, again fails to identify any major advantages in adopting alternative positions in the second stage of labour. The results of a controlled randomized study from these workers (Gardosi *et al.* 1989*b*), using a cushion which enables patients to adopt a squatting position, suggest that this may be beneficial. Both papers provide valuable additional information which needs to be considered carefully when advising women about their delivery.

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A comparison of three methods of assessing inter-observer variation applied to ultrasonic fetal measurement in the third trimester

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Summary. The inter-observer variation of fetal biparietal diameter, head circumference, abdominal circumference, and femoral length measured in the third trimester by ultrasound was studied by three different methods—coefficient of variation, correlation coefficient, and the 95% limits of agreement. The coefficients of variation were 1·6 to 3·7%, the correlation coefficients were 0·89 to 0·98 with *P* values of <0·001, yet the limits of agreement when applied to centile charts were found to be too wide to separate reliably small fetuses from those that were not small. We conclude that the limits of agreement is the preferred method of assessing inter-observer variation, and we suggest that future research into growth retardation move away from ultrasonic measurements of the fetus.

Intrauterine growth retardation is an important cause of perinatal mortality and morbidity and long-term handicap, and yet an efficient screening test for this condition eludes us. Ultrasonic measurements of the fetus in the third trimester have been advocated by some as the preferred method of screening for growth retardation, by direct measurement of the fetus, derived fetal measurements such as the head-to-abdominal circumference ratio, or estimation of the fetal weight. Yet these ultrasonic methods have not become standard practice. In our own institution most of the ultrasonic diagnoses of growth retardation were correct, but many were found to be wrong, often leading to inappropriate treatments. It was this which prompted us to investigate inter-observer variation of third trimester ultrasonic measurements as a possible cause for these wrong results.

Materials and methods

Two of the authors (P.S. and J.M.G.) have a special interest in obstetric ultrasound, and hold two sessions a week at which many fetal measurements are made. These observers have many years experience of ultrasonic fetal measurement in the third trimester. After an initial run-in period during which the rules defining the technique were agreed, the formal part of the study was started. We investigated the inter-observer variation of the following fetal measurements: (a) biparietal diameter; (b) head circumference; (c) abdominal circumference, and (d) femoral length.

These measurements were chosen for study since they are often used, singly or in combination, in formulae to estimate fetal weight by ultrasound. The ultrasound equipment used was a Sonarscan 128 (Diagnostic Sonar, Livingston, Scotland). In measuring the biparietal diameter and head circumference, an image of the head was obtained like an ellipse with the midline

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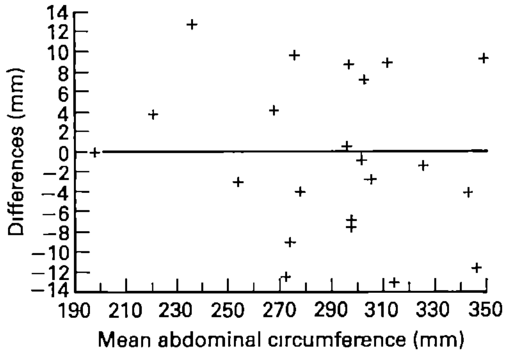

Fig. 1. Scattergram of differences in abdominal circumferences and mean abdominal circumferences.

echo and the cavum septum pellucidum visible. For the abdominal circumference measurements a true transverse section of the abdomen was obtained, showing a transverse section of the spine and the aorta, and the ductus venosus in the middle part of the liver. The femur was measured when both ends of the bone could be seen surrounded by soft tissue; measurements were made between the proximal and distal ends of the diaphysis. Each observer performed the measurements twice in each subject, and the mean of the measurements was used for the analyses. All measurements were made with a light pen.

We performed these measurements in 22 unselected women attending an ordinary antenatal clinic between 24 and 40 weeks gestation. For each type of ultrasonic measurement inter-observer variation was assessed by three different methods: (1) coefficient of variation; (2) correlation coefficient; and (3) limits of agreement.

The inter-observer coefficient of variation is the ratio, expressed as a percentage, of the standard deviation of the differences between two sets of measurements to the mean value of the actual measurements. The correlation coefficient is a widely used statistical tool in obstetrics and requires no further description. Bland & Altman (1986) have argued forcibly that correlation is an inappropriate technique to apply to such data. They have described the method of limits of agreement, which was used by us to investigate the inter-observer variation of measurement of the symphysis–fundal height (Bailey *et al.* 1989). The systematic bias between the observers was calculated, and the 95% confidence intervals (CI) of the limits of agreement were referred to centile charts of biparietal diameter, head circumference, abdominal circumference and femoral length in order to assess the clinical importance of the inter-observer variation. The effects of the limits of agreement on the 50th and 2·3rd centiles were examined, being representative of normal growth and growth retardation respectively. The centile charts at 34 weeks gestation only are presented, this gestational age being typical for screening tests for growth retardation to be undertaken.

Results

Figure 1 shows the differences between the two observers' abdominal circumferences and the actual values of the abdominal circumferences. (The mean of the two observers' abdominal circumferences is taken to represent the actual value of abdominal circumference in each subject.) There is no apparent association between the differences and the actual values of abdominal circumference; therefore in calculating the limits of agreement the data can be analysed directly. Scattergrams of the differences and actual values of biparietal diameter, head circumference and femoral length similarly showed no association between the differences and the actual values.

The results are summarized in Table 1. The coefficients of variation range from 1·6 to 3·7%, and the correlation coefficients from 0·885 to 0·981. All the correlation coefficients are highly statistically significant ($P<0\cdot001$).

Systematic bias between the two observers was assessed by ascertaining whether the mean of the differences between the two sets of observations was significantly different from zero. Bias was only present in the measurement of the femoral length, in which one observer consistently measured less than the other.

Tables 2–5 show the effects of referring the limits of agreement to centile charts of biparietal diameter, head circumference, abdominal circumference, and femoral length. In each instance the limits of agreement were so wide as to seriously impair the effectiveness of these ultrasonic measurements in the measurement of fetal growth in the third trimester. Although the tables refer only to 34 weeks gestation, similar results were obtained for all gestational ages in the third trimester.

Discussion

This investigation confirms the findings of our

Table 1. Correlation coefficients, coefficients of variation and limits of agreement of biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femoral length (FL) All measurements are in cm except femoral lengths which are in mm

	BPD	HC	AC	FL
Correlation coefficient*	0·924	0·955	0·981	0·885
Coefficient of variation (%)	1·6	3·0	2·7	3·7
Differences				
Mean	−0·03	−0·01	−0·06	−1·27
(SD)	(0·27)	(0·89)	(0·77)	(2·26)
Limits of agreement	−0·8 to +0·7	−2·4 to +2·4	−2·2 to +2·0	−7·4 to +4·9
Systematic bias	NS	NS	NS	<0·02

NS, Not significant.
*All P values <0·001

previous study of inter-observer variation, in which we showed that the coefficient of variation and the correlation coefficient are inappropriate methods of assessing inter-observer variation (Bailey *et al.* 1989). Thus in the present study the coefficients of variation were all very small (1·6 to 3·7%) and the correlation coefficients were all close to 1, with P values of <0·001, and yet the measurements did not agree. This study confirms that the only method to assess inter-observer variation is by the method of limits of agreement, since the clinical effects of the inter-observer variation can be assessed directly by referring the limits of agreement to appropriate centile charts.

In this study the limits of agreement were wide, and when referred to centile charts of biparietal diameter, head circumference, abdominal circumference, and femoral length, were too wide to separate reliably small fetuses from those that were not small. It is immaterial which centile charts are used for this purpose, all the ultrasonic measurements studied are normally distributed, and as long as the standard deviation is quoted in the publication which is used for this exercise, then centile charts can be derived from multiples of the standard deviation. Furthermore in the derivation of these centile charts, inter-observer variation is unimportant. Thus if a single observer measures 100 biparietal diameters at 34 weeks gestation he will obtain a mean biparietal diameter and a standard deviation, from which a centile chart can be calculated. If another observer repeated this study in the same 100 women his results would be different, owing to the effects of inter-observer variation; but if there is no systematic bias his mean and standard deviation will be similar, and so will his centile chart. If there is a systematic bias his mean value for the biparietal diameter will be different, but the standard deviation will be similar, and so will the range of values in the centile chart. Inter-observer variation is only important in the measurement of the biparietal diameter in the *individual* patient, and the relation of this measurement to the centile chart. In the individual patient the correct way to assess growth is via longitudinal, not cross-sectional, growth charts. But if at all gestational ages in the third trimester the limits of agreement between observers are wide, then long-

Table 2. Effects of limits of agreement of biparietal diameter (BPD) at 34 weeks gestation

Centiles	BPD (cm)	Limits of agreement
97·7	9·6	
97	9·5	
95	9·4	
90	9·2	
75	9·0	
50	8·7	−0·8 to +0·7 cm = 7·9 to 9·4 cm
25	8·4	
10	8·2	
5	8·0	
3	7·9	
2·3	7·8	−0·8 to +0·7 cm = 7·0 to 8·5 cm

Centile chart derived from Sabbagha *et al.* (1976)

Table 3. Effects of limits of agreement of head circumference (HC) at 34 weeks gestation

Centiles	HC (cm)	Limits of agreement
97·7	32·5	
97	32·4	
95	32·1	
90	31·6	
75	30·8	
50	30·0	−2·4 to +2·4 cm = 27·6 to 32·4 cm
25	29·2	
10	28·4	
5	27·9	
3	27·6	
2·3	27·5	−2·4 to +2·4 cm = 25·1 to 29·9 cm

Centile chart derived from Sabbagha *et al.* (1984).

Table 4. Effects of limits of agreement of abdominal circumference (AC) at 34 weeks gestation

Centiles	AC (cm)	Limits of agreement
97·7	33·5	
97	33·3	
95	32·9	
90	32 3	
75	31·2	
50	30·1	−2·2 to +2·0 cm = 27·9 to 32·1 cm
25	29·0	
10	27·9	
5	27·3	
3	26·9	
2·3	26·7	−2·2 to +2·0 cm = 24·5 to 28·7 cm

Centile chart derived from Tamura & Sabbagha (1980).

itudinal growth charts are going to be difficult to assess.

It may be argued that a study size of 22 was too small, and that a larger study would have resulted in much better agreement. We do not know of any mathematical formula with which to calculate in advance the size of sample required for a study of limits of agreement; yet we feel that the study size was sufficiently large. The limits of agreement depend partly on the standard deviation of the differences between the observations and partly on the sample size. With a larger study the standard deviation is unlikely to change to any significant extent. If we make this assumption and increase the sample size to 100, then the limits of agreement become: (a) biparietal diameter, −0·7 to +0·6 cm; (b) head circumference, −2·0 to +2·0 cm; (c) abdominal circumference, −1·8 to +1·7 cm; (d) femoral length, −6·5 to +3·9 mm.

Referring these new limits of agreement to the centile charts shows that the limits of agreement are still unacceptably wide.

There is a whole obstetric industry devoted to ultrasonic measurement of the fetus in the third trimester, and to the use of these measurements for the assessment of growth retardation, both as screening tests and in patients thought clinically to be at risk of growth retardation. Deter *et al.* (1986) summarized 139 studies of ultrasonic assessment of fetal growth; in only 19 of them was inter-observer variation formally assessed, and none by the method of limits of agreement. The present study puts the clinical value of ultrasonic fetal measurement in serious doubt. Furthermore, it is likely that the inter-observer variation of derived ultrasonic indices using more than one measurement will be even greater, since the errors in measurement will be compounded; thus screening for growth retardation by estimating the head/abdominal circumference ratio (Campbell & Thoms 1977) is likely to be very inaccurate. There are scores of formulae for estimating fetal weight, many of which use multiple ultrasonic indices (Warsof *et al.* 1977; Shepard *et al.* 1982; Thurneau *et al.* 1983; Hadlock *et al.* 1985); the present study shows that all of these methods are liable to be inaccurate. Since many of them require the abdominal circumference to be squared or cubed (Campbell & Wilkin 1975; Higginbottom *et al.* 1975), so will the errors in measurement be squared or cubed, thus increasing the inaccuracy.

These studies give little information on inter-observer variation, and rely heavily on the correlation coefficient to justify their formulae. For example, in the study by Weiner *et al.* (1981) fetal abdominal circumference was measured by static and real-time machines in 39 women, in an attempt to determine whether real-time measurements were as accurate as ones obtained by the static machine. The correlation coefficient was 0·97, and from this the conclusion was drawn that 'it would be unlikely that the AC growth centile (less than the tenth, twenty-fifth to seventy-fifth, greater than the seventy-fifth) would be altered to any clinically significant degree in a late second trimester or third trimester fetus' (by using the real-time machine). This

Table 5. Effects of limits of agreement of femoral length (FL) at 34 weeks gestation

Centiles	FL (mm)	Limits of agreement
97·7	70·1	
97	69·8	
95	69·3	
90	68·5	
75	67·2	
50	65·7	−7·4 to +4·9 mm = 58·3 to 70 6 mm
25	64·2	
10	62·9	
5	62·1	
3	61·6	
2·3	61·3	−7·4 to +4·9 mm = 53·9 to 66·2 mm

Centile chart derived from O'Brien & Queenan (1981).

is one of the few publications where the ultrasonic measurements are actually given; using these data the limits of agreement of static and real-time ultrasonic measurements are −3·4 to +2·8 cm. Referring these limits of agreement to the centile chart of abdominal circumference in Table 4 shows that the agreement is very poor. Since we have no data of inter-observer variation in that study, we do not know whether this poor agreement is due to the instruments used or to the unforeseen effects of inter-observer variation. In the study by Thurneau *et al.* (1983) a formula for estimating fetal weight was derived and applied prospectively to 19 women who were delivered before 34 weeks gestation within 1 week of the ultrasound examination. The correlation coefficient between the estimated fetal weight and the actual birthweight was 0·964, and this information was used to justify the statement 'this simple equation appears to be clinically reliable and easy to use when estimating fetal weight of preterm or low-birth weight fetuses of less than 2500 gm'. Yet from the data given in the paper the limits of agreement between the estimated fetal weight and the actual birthweight were −441 to +422 g. The mean birthweight of the group of babies studied was 1653 g, which results in an average error in estimating fetal weight of about 26%—far greater than was apparent from the text of the publication, and seriously limiting the usefulness of their formula for estimating fetal weight.

We recommend that research into growth retardation move away from ultrasonic fetal measurement, and that if future research involves clinical measurement, then the initial step is to perform a limits of agreement study to assess inter-observer variation.

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A comparison of three methods of assessing inter-observer variation applied to measurement of the symphysis–fundal height

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Summary. This study assesses the inter-observer variation of symphysis–fundal height measurements by three methods—the coefficient of variation, the correlation coefficient and the limits of agreement. The coefficient of variation was 4% and the correlation coefficient 0·959, yet the limits of agreement were very wide. Applying these limits to centile charts of symphysis–fundal height shows that the fundal height cannot be measured by different observers with sufficient agreement to separate small fundal heights from those which are not small, and this severely limits the usefulness of measurement of the symphysis–fundal height as a screening test for intrauterine growth retardation. We conclude that inter-observer variation should be assessed by the method of limits of agreement, and not by calculating the coefficient of variation or the correlation coefficient.

Measurement of the symphysis–fundal height has become established practice in many maternity units as the preferred way of screening for intrauterine growth retardation, arguments in its favour being its speed, cheapness and general applicability Yet examination of published reports of fundal height measurement shows a wide variation in its performance, the sensitivity of the method ranging from 27 to 86% (Table 1). One possible reason for this wide variation in performance is inter-observer variation, and this prompted us to investigate inter-observer variation in detail. The usual ways of assessing inter-observer variation to be found in published work are the coefficient of variation and the correlation coefficient. We describe a new concept in assessing inter-observer variation, using a statistical technique first described by Bland & Altman (1986).

Materials and methods

Two observers, both practising obstetricians with many years' experience of the technique, measured in a standardized fashion the symphysis–fundal heights of 39 unselected women attending an ordinary antenatal clinic between 20 and 40 weeks gestation. The sample size was chosen arbitrarily, being the number of women

Table 1. Performance of symphysis-fundal height as a screening test for intrauterine growth retardation

Study	Sensitivity	Study size
Quaranta *et al.* (1981)	30/41 (73%)	138
Belizan *et al* (1978)	38/44 (86%)	139
Mathai *et al.* (1987)	47/59 (80%)	358
Calvert *et al.* (1982)	29/45 (64%)	381
Westin (1977)	32/47 (68%)	428
Cnattingius *et al.* (1984)	34/59 (58%)	527
Pearce & Campbell (1987)	76/100 (76%)	699
Rosenberg *et al* (1982)	28/50 (56%)	753
Wallin *et al.* (1981)	60/97 (62%)	812
Persson *et al* (1986)	70/263 (27%)	2941

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attending two consecutive antenatal clinics. Each observer measured the fundal height in each subject twice, and the mean of these measurements was taken to represent the fundal height obtained by each observer in each subject (Table 2). Inter-observer variation was assessed by three methods: (a) coefficient of variation; (b) correlation coefficient; and (c) limits of agreement.

The correlation coefficient is a widely used statistical tool and requires no further description. The coefficient of variation in any sample is the ratio, expressed as a percentage, of the standard deviation and the mean value of the sample, and is commonly used to assess inter-observer variation. In this context the usual practice is for many observers to measure the same subject, and the inter-observer coefficient of variation to be calculated (for example, Calvert *et al.* 1982). In this study, with two observers and 39 subjects, the inter-observer coefficient of variation was calculated from the ratio, expressed as a percentage, of the standard deviation of the differences between the two sets of measurements and the mean fundal height for the whole study.

Table 2. Symphysis–fundal heights (cm) measured by two observers

Subject	Observer A	Observer B	Differences (A−B)
1	32·5	34·8	−2·3
2	26·0	28·7	−2·7
3	24·2	25·7	−1·5
4	32·2	35·8	−3·6
5	39·5	41·7	−2·2
6	33·4	32·5	+0·9
7	30·8	31·3	−0·5
8	34·4	35·4	−1·0
9	30·8	33·4	−2·6
10	29·9	33·2	−3·3
11	32·3	33·7	−1·4
12	29·1	31·1	−2·0
13	27·8	28·7	−0·9
14	32·1	33·6	−1·5
15	25·6	29·0	−3·4
16	28·0	30·3	−2·3
17	31·0	32·7	−1·7
18	28·7	30·1	−1·4
19	34·9	37·0	−2·1
20	32·0	34·4	−2·4
21	35·6	34·8	+0·8
22	30·8	32·1	−1·3
23	25·8	26·1	−0·3
24	16·5	19·0	−2·5
25	33·1	35·2	−2·1
26	31·9	34·0	−2·1
27	34·6	36·9	−2·3
28	34·8	36·4	−1·6
29	21·5	24·3	−2·8
30	27·1	32·0	−4·9
31	35·0	34·4	+0·6
32	35·4	36·5	−1·1
33	32·7	35·3	−2·6
34	38·1	39·5	−1·4
35	35·6	34·6	+1·0
36	35·5	35·0	+0·5
37	32·6	33·4	−0·8
38	34·6	37·5	−2·9
39	36·0	37·2	−1·2

Calculation of the limits of agreement was described by Bland & Altman (1986). These authors used this method to investigate the agreement between two instruments (a Wright peak-flow meter and a mini peak-flow meter) in the same group of subjects measured by the same observer, but the same statistical technique can be used to investigate the agreement between two observers using the same instrument in the same group of subjects, the instrument in this case being the centimetre tape to measure the symphysis–fundal heights. Calculation of the limits of agreement is now described.

All the fundal heights measured are listed in Table 2. The figures in the last column, the differences, *d*, are obtained by subtracting observer B's fundal heights from those of observer A, and allow the relation of the differences to the actual values of the fundal heights to be examined. Since we do not know the actual value of the symphysis–fundal height in each subject, we have taken the mean of the two observers' measurements for each subject. Figure 1 shows that there is no apparent relation between the differences and the means of the observers' fundal heights, and so we can analyse the differences directly. If there had been an association between the differences and the means of the observers' fundal heights, logarithmic transformation of the data may have yielded a scattergram more like Fig. 1, such that we can apply the analysis described below to the log-transformed data.

The next step is to calculate mean difference (d) and the standard deviation of the differences (s), and from these we can estimate the limits of agreement being the mean ± 1·96 SD (Table 3). These are the limits of agreement of the sample of 39 women; in order to estimate the limits of agreement of the whole antenatal population we

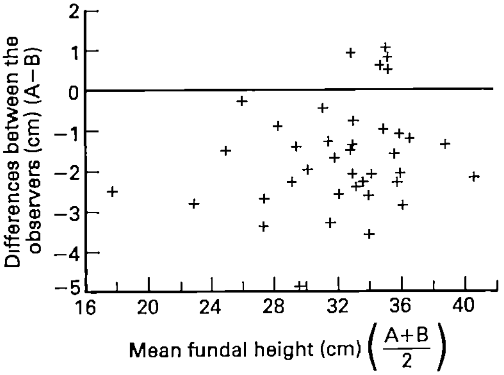

Fig. 1. Scattergram of differences in the observers' fundal heights and the means of the observers' fundal heights.

have to calculate the 95% confidence intervals (CI) of the limits of agreement of the sample of 39 women. The standard error of the limits of agreement is approximately $\sqrt{3s^2/n}$. We multiply this standard error by the value in the t table at $n-1$ degrees of freedom at the 5% level of significance. The 95% CI of the upper limit of agreement is the value of the upper limit ± t times the standard error; and the 95% CI of the lower limit of agreement is the value of the lower limit ± t times the standard error.

The 95% CI of the limits of agreement express the uncertainty of the study limits of agreement as estimates of the limits of agreement for the whole antenatal population. In the clinical interpretation of the limits of agreement, however, we thought it safer to take the extremities of the 95% CI for the upper and lower limits of agreement to represent the true limits of agreement, being the worst possible scenario.

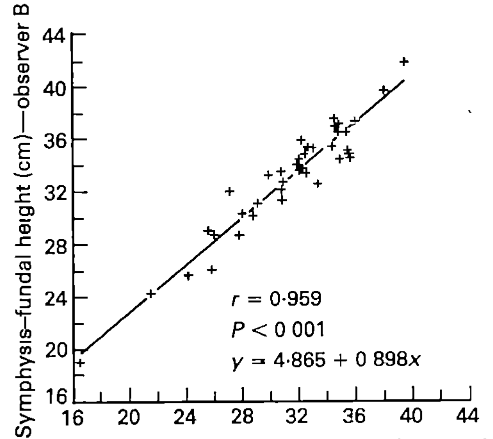

Fig. 2. Correlation between the two observers' fundal heights.

Results

Errors in clinical measurement can be systematic, where one observer's method of measurement is different from the other's, even though this difference in technique may not be obvious; or random, where the errors are out of the control of the observers. Inspection of the data in Table 2 shows that observer A consistently measured the fundal heights to be less than observer B. Mathematically, systematic bias is assessed by ascertaining whether the mean difference between the two sets of measurements is statistically different from zero In this study the mean difference is highly statistically different from zero (t = 8·167; P<0·001). This systematic bias is important in the interpretation of the results of the limits of agreement.

The coefficient of variation was calculated from the standard deviation of the differences between the two sets of measurements divided by the mean fundal height for the whole study, multiplied by 100: that is, 1·3/32·2×100 = 4·0%; the correlation coefficient was 0·959, P<0·001 (Fig.2); and the 95% limits of agreement were −5·0 to +1·6 cm (the phrase 'limits of agreement' appearing subsequently is taken to imply 95% limits of agreement).

What do these limits of agreement mean? Is this good agreement or not? The only way to find this out is to refer the limits of agreement to centile charts of symphysis–fundal height. Table 4

Table 3. Calculation of the limits of agreement

n	=39
Mean difference (d)	=−1·7 cm
Standard deviation (s)	=1·3 cm
Limits of agreement (d±1.96s)	=−4·2 to +0·8 cm

Standard error of limits of agreement = $\sqrt{3s^2/n}$
= 0 4 cm

Find value in t table at $n-1$ degrees of freedom at 5% level of significance and multiply this value by the standard error
=2·042×0·4
=0·8 cm

95% CI of upper limit of agreement=+0·8±0·8 cm
=0 to +1·6 cm

95% CI of lower limit of agreement=−4·2±0·8 cm
=−5·0 to −3·4 cm

true limits of agreement =−5·0 to +1·6 cm

Table 4. Effects of limits of agreement on symphysis–fundal height (cm) at 25, 30 and 35 weeks gestation*

Centiles	Fundal height	Limits of agreement
25 weeks gestation (*n*=1284)		
97·7	28·2	
97	27·9	
95	27·3	
90	26·4	
75	25·0	
50	23·4	−5·0 to +1·6 cm = 18·4 to 25·0 cm
25	21·8	
10	20·4	
5	19·5	
3	18·9	
2·3	18·6	−5·0 to +1·6 cm = 13·6 to 20·2 cm
30 weeks gestation (*n*=1405)		
97·7	32·9	
97	32·7	
95	32·1	
90	31·3	
75	29·9	
50	28·3	−5·0 to +1·6 cm = 23·3 to 29·9 cm
25	26·7	
10	25·3	
5	24·5	
3	23·9	
2·3	23·7	−5·0 to +1·6 cm = 18·7 to 25·3 cm
35 weeks gestation (*n*=1521)		
97·7	37·8	
97	37·5	
95	36·9	
90	36·0	
75	34·5	
50	32·8	−5·0 to +1·6 cm = 27·8 to 34·4 cm
25	31·1	
10	29·6	
5	28·7	
3	28·1	
2·3	27·8	−5·0 to +1·6 cm = 22·8 to 29·4 cm

*Centile charts derived from Persson *et al.* (1986)

shows the centile values of symphysis–fundal height at 25, 30 and 35 weeks gestation, from the large study reported by Persson *et al.* (1986). The Table shows the effect of applying the limits of agreement to a group of fundal heights which are normal. The 50th centile represents a group of fundal heights which are normal: they are average. Overestimating the values for the 50th centile by the upper limit of agreement results in fundal heights which are near the 75th centile, and may still be considered normal; but underestimating the values for the 50th centile by the lower limit of agreement results in fundal heights below the 2·3rd centile, and this may lead to unnecessary interventions for supposed growth retardation where no growth retardation exists.

Table 4 also shows the effects of applying the limits of agreement to a group of fundal heights which are very small: below the 2·3rd centile. Most of these fundal heights are small for pathological reasons, such as growth retardation, and their reliable identification is important. Underestimating the values for the 2·3rd centile by the lower limit of agreement results in fundal heights which are still very small, and overestimating the 2·3rd centile by the upper limit of agreement results in fundal heights near the 10th centile, which may be considered still small. But as we have seen, there was a considerable systematic bias in the measurements, with one observer either consistently overestimating the fundal heights or the other observer underestimating them—we do not know which. Furthermore we arbitrarily subtracted observer B's fundal heights from those of observer A; if we had subtracted observer A's fundal heights from those of observer B we would have obtained the same limits of agreement, except that the signs would have been different—that is, +5·0 to −1·6 cm. Now, overestimating the value for the 50th centiles by the upper limit of agreement results in fundal heights above the 97th centile, which may lead to unnecessary investigations for supposed twins, hydramnios or macrosomia; and overestimating the values for the 2·3rd centile by the upper limit of agreement results in fundal heights above the 50th centile, and so the diagnosis of severe growth retardation would be missed.

To test the hypothesis that the method of measurement of symphysis–fundal height was imperfect, the experiment was repeated using an alternative method, but the results were similar (Table 5; method 1—position of the fundus located and marked with a pen, the fundal height being measured from the symphysis pubis to the ink mark; method 2—end of measuring tape held by the heel of the hand positioned at the fundus and the distance to the symphysis–pubis measured). To test the hypothesis that one of the observers just was not good at measuring the symphysis–fundal heights the experiment was repeated with a third observer, who had a similar experience of the technique; but similar wide

Table 5. Limits of agreement of symphysis–fundal height—effects of different method and third observer

	Limits of agreement
Method 1 (*n*=39)	−5·0 to +1·6 cm
Method 2 (*n*=20)	−6·1 to +2·4 cm
Observers A and B (*n*=39)*	−5·0 to +1·6 cm
Observers A and C (*n*=20)*	−4·1 to +3·4 cm
Observers B and C (*n*=20)*	−3·3 to +3·8 cm

*All using method 1.

Method 1—fundus located with pen, measurement from symphysis–pubis to pen mark.

Method 2—fundus located with heel of hand, measurement from heel of hand to symphysis–pubis.

95% limits of agreement were obtained with all three pairs of observers (Table 5).

Thus throughout the whole gestational age range at which screening for growth retardation is important, and using an alternative method of measurement and a third observer, the limits of agreement are wide, and seriously impair the effectiveness of measurement of the symphysis–fundal height as a screening test for growth retardation. Only if the fundal height were well below the 2·3rd centile would both observers agree, in 95% of cases, that the fundal height was small. These limits of agreement were interpreted taking the extremities of the 95% CI for the upper and lower limits of agreement, being the worst possible scenario; even if a more optimistic interpretation of the limits of agreement were made, by taking the 95% CI nearest to zero, the limits of agreement are still unacceptably wide (± 3·4 cm, Table 3).

Discussion

This study shows that the coefficient of variation was 4%, which may seem small. But when one examines the literature which uses the coefficient of variation as the method of assessing inter-observer variation, it is nearly always less than 10%. This is not surprising, since the inter-observer coefficient of variation is the ratio, expressed as a percentage, of the standard deviation of the *differences* between two sets of measurements and the mean value of the *actual* measurements; therefore the coefficient of variation will always be small, even when the measurements do not agree, as in this study. Another common way of assessing inter-observer variation is to calculate the correlation coefficient; it is assumed that the closer this is to 1 the better the agreement between the two sets of measurements. Yet this is not so; the correlation coefficient investigates the statistical association between two sets of measurements, but not their agreement. Indeed it would be surprising if there were no statistical association between two sets of measurements in the same group of subjects using the same measuring instrument. Thus it is possible as in this study that the correlation coefficient is close to 1, and yet the measurements do not agree. Figure 2 shows a scattergram of the two observers' fundal heights, with the regression line drawn in. This use of a scattergram and regression line, with the correlation coefficient calculated, is common in published work on inter-observer variation, and may give a false sense of agreement where no agreement exists. This inappropriate use of the correlation coefficient to assess agreement has been stressed by Bland & Altman (1986). Therefore the coefficient of variation and the correlation coefficient are not the correct methods to assess inter-observer variation.

Another reason for preferring the method of limits of agreement is that the clinical effects of the inter-observer variation can be easily assessed by referring the limits of agreement to centile charts. This cannot be done with the coefficient of variation or the correlation coefficient Persson's centile charts were chosen for this exercise since, unlike other publications on measurement of the symphysis–fundal height, it was possible to calculate the standard deviation of the fundal heights at 25, 30 and 35 weeks gestation; furthermore, we could deduce from the information given that fundal heights were normally distributed. Therefore it was possible to calculate centile charts from multiples of the standard deviation. (The other publications merely drew smoothed 10th, 50th and 90th centiles.) Note that the clinical effects of the limits of agreement are partly dependent on the width of the limits of agreement and partly on the normal range of values on the centile chart. The biological variation of symphysis–fundal height at any gestational age is narrow, the ratio of the +2 SD value to the −2 SD value being about 1·5/1. In another biological system with a much wider normal range, apparently wide limits of agreement may be sufficiently narrow to separate small members of the population from those that are not small.

This concept of limits of agreement is fundamental to all clinical research involving measurement. It is common for articles to be accepted for publication where only one or two observers have been involved in the research. If inter-observer variation has been assessed it is nearly always by calculating the coefficient of variation or the correlation coefficient. If the researchers are sufficiently influential their research may become standard practice. Later researchers may be unable to replicate the results of the original work, owing to the unforeseen effects of inter-observer variation, and the original work may be discredited. This cycle of enthusiasm followed by disillusion is common in clinical research, and in work involving measurement, inter-observer variation is an important cause of this disillusion. The fundal height studies are an example of this cycle.

We conclude that calculating the limits of agreement, and not the coefficient of variation or the correlation coefficient, is the preferred method of assessing inter-observer variation in clinical measurement. Furthermore this study shows that it is not possible for different observers to measure the symphysis–fundal height with sufficient agreement to separate reliably small fundal heights from those that are not small.

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The Southmead perineal suture study. A randomized comparison of suture materials and suturing techniques for repair of perineal trauma

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Summary. Commonly used suture materials and techniques for perineal repair following vaginal delivery were compared in a randomized controlled trial involving 1574 women. Three comparisons were made using a modified factorial design. In the comparison of teflon-coated polyglycolic acid (Dexon plus) with chromic catgut for repair of the vagina and deep perineal tissues there was no clear difference other than less short-term analgesia being required in association with polyglycolic acid. Outcome was also similar after skin repair with either polyglycolic acid or chromic catgut or silk, although silk repair required more packets of material and was associated with delay in resuming sexual intercourse; polyglycolic acid was more likely to need removal than chromic catgut but it appeared to reduce the need for resuturing. There was no clear difference between continuous subcuticular and interrupted transcutaneous sutures for repair of perineal skin.

In Britain as many as 70% of women are likely to require repair of perineal trauma following childbirth (Sleep *et al.* 1984). As might be expected, most of these women experience some perineal pain or discomfort in the immediate postpartum period, but even 3 months later, as many as 20% still have problems (such as dyspareunia) likely to be related to the injury and its repair.

In addition to the nature and extent of the trauma, the technique of repair and choice of suture material are likely to have a bearing on the extent of this morbidity. But there is no consensus about which suture materials to use for the deeper tissues and for the skin, and which technique of skin closure to use (Grant 1986). This randomized controlled trial aimed to clarify the best approach to perineal repair by comparing the effects of different suture materials and suturing techniques on both short- and long-term complications.

Patients and methods

The study was conducted at Southmead Hospital, Bristol, and had the approval of the local hospital research and ethics committee. Over a 9-month period, women booked for delivery in the hospital were given a written description of

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Table 1. Polyglycolic acid (Dexon plus) versus chromic catgut for repair of the vagina and deep perineal tissues—description of the groups at entry and of the repair of the injury

	Polyglycolic acid (n = 796)	Chromic catgut (n = 778)
Description of groups at entry		
Maternal age (years) Mean (SD)	26·0 (4·9)	26·1 (4·9)
Married	655 (82)	655 (84)
Primiparous	421 (53)	391 (50)
Operative vaginal delivery	186 (23)	176 (23)
Birthweight (g) Mean (SD)	3371 (488)	3350 (475)
Perineal injury		
Episiotomy alone	390 (49)	407 (52)
Episiotomy + extension	100 (13)	96 (12)
Tear	306 (38)	275 (35)
Repair of injury		
Materials actually used		
Vagina + deep tissues		
Polyglycolic acid	743 (93)	15 (2)
Chromic catgut	52 (7)	760 (98)
None	1 (0)	3 (0)
Perineal skin		
Polyglycolic acid	276 (35)	217 (28)
Chromic catgut	241 (30)	281 (36)
Silk	245 (31)	238 (31)
None	34 (4)	42 (5)
Technique of skin closure		
Subcuticular	197 (25)	192 (25)
Interrupted	545 (68)	521 (67)
Subcuticular + interrupted	26 (3)	29 (4)
'None'	28 (3)	36 (4)
Operator		
Midwife	237 (30)	234 (30)
Senior house officer	439 (55)	443 (57)
General practitioner	34 (4)	26 (3)
Registrar/consultant	84 (11)	73 (9)
Medical student	2 (0)	2 (0)
Packets opened to complete repair Mean (SD)	2·2 (0·7)	2·2 (0·7)
Time taken to complete repair (min) Mean (SD)	15·8 (7·3)	15·3 (7·5)

Results are n (%) or mean (SD) values as appropriate

the trial when they were in the last trimester of pregnancy. Following delivery women requiring perineal repair, who agreed to participate, were randomly allocated to a particular policy for repair. The woman's name and entry details were first written on to a form printed on the outside of the next available, serially numbered, sealed, opaque envelope; then the envelope was opened. Each envelope contained the allocated materials and instruction for their use

The study used a modified 2 × 3 × 2 factorial design to compare:

(a) Two absorbable materials for repair of the vagina and deep perineal tissues—polyglycolic acid with a teflon coating (Dexon plus), 2–0 on a 30-mm, half-circle, multipurpose needle (Davis & Geck Ltd); and chromic catgut 2–0, on a 35-mm taper cut, half-circle needle (Ethicon Ltd).

(b) Three materials for repair of perineal skin—Dexon plus and chromic catgut, as above; and a non-absorbable material, black silk 2–0 on a 35-mm curved, reversed cutting needle (Ethicon Ltd).

(c) Two suturing techniques for closure of the skin by absorbable material—subcuticular continuous and transcutaneous interrupted techniques.

Table 2. Polyglycolic acid (Dexon plus) versus chromic catgut for repair of the vagina and deep perineal tissues—outcome

	Polyglycolic acid *n* (%)	Chromic catgut *n* (%)
At 2 days postpartum	(*n* = 768)	(*n* = 752)
Perineal pain 'now'	373 (49)	387 (51)
Oral analgesia in previous 24 h	368 (48)	403 (54)*
At 10 days postpartum	(*n* = 679)	(*n* = 670)
Pain in last 24 h		
None	475 (70)	452 (67)
Mild	128 (19)	129 (19)
Moderate	63 (9)	77 (11)
Severe	10 (1)	13 (2)
Oral analgesia 'today'	52 (8)	62 (9)
At 3 months postpartum	(*n* = 687)	(*n* = 679)
Pain in last 24 h		
None	607 (88)	595 (88)
Mild	61 (9)	61 (9)
Moderate	15 (2)	18 (3)
Severe	3 (0)	4 (1)
Sexual intercourse not resumed	83 (12)	74 (11)
Dyspareunia, if resumed	156 (23)	148 (22)
Absorbable suture material removed	174 (25)	143 (21)
Resutured	7 (1)	6 (1)

* $P<0{\cdot}05$.

The three principal analyses were of the 'main effects' of these comparisons, making the assumption that the factorial design balanced other differences in the repair between the groups.

Trauma to the vagina was repaired with a continuous suture. Deeper perineal tissues were usually apposed with interrupted sutures.

Details of the injury and repair were recorded by the operator immediately after completion of the repair. Pain, analgesia use and wound healing were assessed by staff on the postnatal ward (or by the community midwife if the woman was already at home) 2 days after delivery. A further assessment was made 10 days postpartum by the mother in respect of perineal pain, and by the community midwife in respect of perineal healing.

Three months after delivery a self-administered questionnaire was sent to all women who participated, enquiring about perineal pain, time to resumption of sexual intercourse, dyspareunia and general well-being If a questionnaire was not returned within 2 weeks, contact was made by telephone or via the community midwife or health visitor

Fully 'blind' assessment of outcome was not possible because there are obvious differences between the materials and closure techniques. However, details of the trial's design, including the main hypotheses to be tested, were kept confidential.

The two principal measures of outcome were perineal pain on the 10th day and dyspareunia at 3 months after delivery. Expected rates for women whose perineal trauma was repaired with chromic catgut for all layers were 24% and 20% respectively (based on Spencer *et al.* 1986). The preset trial size of 1500 women had an 80% chance of showing a statistically significant difference if the real difference in the prevalence of these outcomes was 4·0–4·5% in the comparison of the two materials for the deep tissues, and 7·0–7·5% for the other two comparisons. Primary analyses were based on the group as allocated because these comparisons are free of selection bias. χ^2, Fisher's exact and Student's *t*-tests and one-way analysis of variance were used, as appropriate. There were no interim analyses.

Results

Overall, 1574 women participated. A further 22 envelopes were unaccounted for but these

Table 3. Polyglycolic acid (Dexon plus) versus chromic catgut versus silk for perineal skin closure—description of the groups at entry and of the repair of the injury

	Polyglycolic acid (*n* = 535)	Chromic catgut (*n* = 522)	Silk (*n* = 517)
Description of groups at entry			
Maternal age (years) Mean (SD)	26·1 (5·0)	26·2 (4·8)	26·2 (4·9)
Married	444 (83)	435 (83)	431 (83)
Primiparous	277 (52)	265 (51)	270 (52)
Operative vaginal delivery	142 (27)	109 (21)	111 (21)
Birthweight (g) Mean (SD)	3386 (480)	3338 (472)	3358 (488)
Perineal injury			
Episiotomy alone	277 (52)	262 (50)	258 (50)
Episiotomy + extension	70 (13)	66 (13)	60 (12)
Tear	188 (35)	194 (37)	199 (38)
Repair of injury			
Materials actually used			
Perineal skin			
Polyglycolic acid	465 (87)	16 (3)	12 (2)
Chromic catgut	36 (7)	471 (90)	15 (3)
Silk	10 (2)	11 (2)	462 (89)
None	24 (4)	24 (5)	28 (5)
Vagina + deep tissues			
Polyglycolic acid	276 (52)	232 (44)	250 (48)
Chromic catgut	258 (48)	289 (55)	265 (51)
None	1 (0)	1 (0)	2 (0)
Technique of skin closure			
Subcuticular	194 (36)	189 (36)	6 (1)
Interrupted	291 (54)	290 (56)	485 (93)
Subcuticular + interrupted	30 (6)	23 (4)	2 (0)
'None'	20 (3)	20 (3)	24 (4)
Operator			
Midwife	152 (28)	156 (30)	161 (31)
Senior house officer	302 (57)	307 (59)	275 (53)
General practitioner	14 (3)	18 (3)	28 (5)
Registrar/consultant	65 (12)	40 (8)	52 (10)
Medical student	2 (0)	1 (0)	1 (0)
Packets opened to complete repair/ woman Mean (SD)	2·21 (0·76)	2·13 (0·69)	2·31 (0·74)*
Time taken to complete repair/woman (min) Mean (SD)	16·0 (7·8)	15·2 (6·9)	15·4 (7·6)

* $P<0{\cdot}05$.

Results are *n* (%) or mean (SD) values as appropriate

showed no preponderance of any particular allocation. Questionnaires for the assessments on the 2nd day, 10th day and at 3 months were returned for 1520 (97%), 1349 (86%), and 1366 (87%) women respectively.

Comparison of polyglycolic acid (n = 796) with chromic catgut (n = 778) for repair of the vagina and deep perineal tissues

The two groups were comparable at entry in important respects (Table 1). The material allocated for repair of the vagina and deep perineal tissues was actually used for 93% of those in the polyglycolic acid group and 98% of those in the chromic catgut group.

There was a tendency for the material allocated for the deep tissues to be used for the skin when not actually allocated for this purpose. Other aspects of the repair were similar in the two groups (Table 1)

Women in the polyglycolic acid group used less oral analgesia in the immediate postpartum period ($\chi^2 = 4{\cdot}88$, 1 d.f., $P = 0{\cdot}03$, relative risk

Table 4. Polyglycolic acid (Dexon plus) versus chromic catgut versus silk for perineal skin closure—outcome

	Polyglycolic acid n (%)	Chromic catgut n (%)	Silk n (%)
At 2 days postpartum	(n = 519)	(n = 505)	(n = 498)
Perineal pain 'now'	253 (49)	252 (50)	255 (51)
Oral analgesia in previous 24 h	256 (49)	259(51)	256 (51)
At 10 days postpartum	(n = 450)	(n = 458)	(n = 444)
Pain in last 24 h			
None	307 (68)	322 (70)	303 (68)
Mild	84 (19)	88 (19)	85 (19)
Moderate	53 (12)	40 (9)	47 (11)
Severe	6 (1)	8 (2)	9 (2)
Oral analgesia 'today'	35 (8)	39 (9)	40 (9)
At 3 months postpartum	(n = 458)	(n = 458)	(n = 450)
Perineal pain in last week			
None	402 (88)	405 (88)	397 (88)
Mild	43 (9)	40 (9)	39 (9)
Moderate	9 (2)	12 (3)	12 (3)
Severe	4 (1)	1 (0)	2 (0)
Sexual intercourse not resumed	52 (11)	40 (9)*	66 (15)*
Dyspareunia, if resumed	105 (23)	105 (23)	94 (21)
Absorbable material removed	180 (39)	107 (23)	30 (7)***
Resutured	1 (0)	5 (1)	7 (2)

* P<0·05; *** P<0·001.

= 0·9, 95% CI 0·8 to 1·0) and were more likely to report that some absorbable material had been removed (χ^2 = 3·54, 1 d.f., P = 0·06, relative risk = 1·2, 95% CI 1·0 to 1·5); otherwise the outcome was very similar in the two groups (Table 2). Clinically assessed oedema, bruising and healing were also similar in the two groups, 2 and 10 days after delivery.

Comparison of polyglycolic acid (n = 535), chromic catgut (n = 522) and silk (n = 517) for repair of the perineal skin

The three groups were generally similar at entry although the women in the polyglycolic acid group had somewhat heavier babies and more operative vaginal deliveries (Table 3). A material other than the one allocated was used for skin closure for 9% of women in the polyglycolic acid group and for 5% of women in the other two groups. There was a tendency for the material allocated for the skin also to be used for the deep tissue, contrary to the allocation. The skin closure techniques and operators were similar.

There were significant differences between the groups in the numbers of packets opened to complete the repair, the largest number when the allocation was to silk (Table 3). When the same absorbable material was used for the deep layers as well as for the skin these rates were even lower: 2·13 (polyglycolic acid) and 2·03 (chromic catgut).

There were no differences between the groups in the principal measures of outcome; but women allocated to the silk group tended to resume sexual intercourse later (Table 4). Women in the polyglycolic acid group were much more likely to report that some absorbable material had been removed. But resuturing was less common in this group, although this difference was not conventionally significant.

Comparison of continuous, subcuticular (n = 533) and transdermal, interrupted (n = 524) suturing for closure of the perineal skin

Some characteristics of the groups at entry are described in Table 5. Women allocated to the 'interrupted' policy were more likely to have extensions of an episiotomy and this was reflected in more extensive damage to both the vagina and the perineum. Of those allocated subcuticular closure, 18% had only interrupted

Table 5. Continuous subcuticular versus interrupted transcutaneous suturing for closure of the perineal skin—description of the groups at entry and of the repair of the injury

	Subcuticular (n = 533)	Interrupted (n = 524)
Description of groups at entry		
Maternal age (years) Mean (SD)	26·0 (4·8)	25·9 (5·0)
Married	443 (83)	436 (83)
Primiparous	256 (48)	286 (55)
Operative vaginal delivery	123 (23)	124 (23)
Birthweight (g) Mean (SD)	3383 (477)	3341 (480)
Perineal injury		
Episiotomy alone	289 (54)	250 (48)
Episiotomy + extension	53 (10)	83 (16)
Tear	191 (36)	191 (37)
Repair of injury		
Technique of skin closure		
Subcuticular	371 (70)	12 (2)
Interrupted	94 (18)	487 (93)
Subcuticular + interrupted	50 (9)	3 (1)
'None'	18 (3)	22 (4)
Materials used for skin closure		
Polyglycolic acid	243 (46)	238 (45)
Chromic catgut	259 (49)	248 (48)
Silk	9 (2)	12 (2)
None	22 (4)	26 (5)
Materials used for vagina and deep tissues		
Polyglycolic acid	259 (49)	249 (48)
Chromic catgut	273 (51)	274 (52)
None	1 (0)	1 (0)
Operator*		
Midwife	132 (25)	176 (34)
Senior house officer	332 (64)	277 (53)
General practitioner	17 (3)	15 (3)
Registrar/consultant	50 (9)	55 (11)
Medical student	2 (0)	1 (0)
Packets opened to complete repair/woman		
Mean (SD)	2·15 (0·71)	2·20 (0·75)
Time taken to complete repair/woman (min)		
Mean (SD)	15·6 (7·2)	15·6 (7·6)

* P<0·05.

Results are n (%) or mean (SD) values as appropriate.

sutures; but some of these women had either small or ragged skin trauma making interrupted sutures clinically more appropriate. Only 2% of those allocated interrupted suturing were repaired with a subcuticular suture (Table 5). The materials used for the deep tissues were very similar in the two groups. Some midwives preferred the interrupted technique. This is a further reason for the non-compliance with the allocated technique and also why fewer women in the subcuticular group were actually sutured by a midwife. Sometimes a midwife called a senior house officer if the allocation was to subcuticular suturing

There were no clear differences between the groups in outcome, other than interrupted suturing being associated with a greater need to remove material (Table 6). In the subcuticular group 4% fewer women had pain at 10 days postpartum, but this difference was not statistically significant. The higher dyspareunia rate observed in the subcuticular group is potentially misleading because more women in this group had actually resumed intercourse. Failure to

Table 6. Continuous subcuticular versus interrupted transcutaneous suturing for closure of the perineal skin—outcome

	Subcuticular *n* (%)	Interrupted *n* (%)
At 2 days postpartum	(*n* = 509)	(*n* = 515)
Perineal pain 'now'	255 (50)	250 (49)
Oral analgesia in previous 24 h	266 (52)	249 (48)
At 10 days postpartum	(*n* = 447)	(*n* = 461)
Pain in last 24 h		
None	317 (71)	311 (67)
Mild	75 (17)	97 (21)
Moderate	46 (10)	47 (10)
Severe	8 (2)	6 (1)
Oral analgesia 'today'	33 (7)	41 (9)
At 3 months postpartum	(*n* = 465)	(*n* = 451)
Perineal pain in last week		
None	407 (88)	400 (89)
Mild	48 (10)	35 (8)
Moderate	7 (2)	14 (3)
Severe	3 (1)	2 (0)
Sexual intercourse not resumed	41 (9)	50 (11)
Dyspareunia, if resumed	116 (25)	94 (21)
Absorbable material removed	121 (26)	166 (37)***
Resutured	3 (1)	3 (1)

***$P<0\cdot001$

have resumed pain-free intercourse was almost equally common in the two groups (34% *vs* 33%). Three women in each group reported that they had been resutured.

Discussion

There is variation in the materials and techniques utilized for perineal repair, but the various combinations used in this trial do include the most popular approaches currently employed (Grant 1989*a*). Before the trial the preference in Southmead Maternity Hospital was to use chromic catgut to the deep tissues and chromic catgut or silk in interrupted sutures to close the skin. Yet, on the basis of the published experimental data on perineal suturing (Grant 1986), the choice of polyglycolic acid for all layers with a subcuticular suture to the skin seemed a preferable policy.

Vagina and deep tissue repair

The Southmead study is the only randomized trial to address in isolation the question of which absorbable material should be used to repair the vagina and deeper tissues; in other trials this question has been subsumed in a comparison of materials used for all layers. In the Southmead suture study there appeared to be little to choose between polyglycolic acid and chromic catgut for repair of the deeper tissues although the use of polyglycolic acid was associated with a reduced requirement for pain relief in the immediate postpartum period. This is consistent with the pattern seen in the trials (Tompkins & Lea 1972; Beard *et al.* 1974; Livingstone *et al.* 1974; Rogers 1974; Banninger *et al.* 1978; Roberts & McKay Hart 1983) which assessed polyglycolic acid in comparison with chromic catgut when both were used for all layers. These trials all suggest that polyglycolic acid is associated with less pain and reduced analgesia requirement in the early puerperium (Grant 1989*b*).

Skin repair suture material

However, the Southmead comparison of polyglycolic acid with chromic catgut for repair of the perineal skin does not show this difference; the two materials also seem equivalent in the longer term: polyglycolic acid sutures seem to reduce the need for resuturing (and this is consistent with the other trials) but also seem to be associated with a later resumption of sexual intercourse (comparable data are not available in other trials).

The Southmead trial did not suggest any advantage for silk, although, unlike comparable trials (Hansen *et al.* 1975; Bendsen & Madsen 1980; Buchan & Nicholls 1980), it did not show increased pain in the short term associated with silk (Grant 1989*b*). In the longer term, however, silk was associated with a delay to resume sexual intercourse and with more frequent resuturing. This latter finding is consistent with the comparable trials. The lower cost per packet of silk is offset by the larger number of packets opened and the need for the silk to be removed in the puerperium.

No clear difference in outcome emerged in the trial reported here between the policies of subcuticular and interrupted sutures for perineal skin repair. However, an overview by Grant (1989*b*) of all relevant trials (Banninger *et al.* 1978; Detlefson *et al.* 1980; Isager-Sally *et al.* 1986, and the present study) suggests less perineal pain after subcuticular suturing with the possibility that this may also be reflected in a lower prevalence of pain and longer-term dyspareunia.

The point estimates derived from the Southmead trial do not appear to be in line with those of comparable trials in some important respects, but these seeming inconsistencies may be due to chance, as there is overlap between their confidence intervals. Another explanation is that polyglycolic acid and the subcuticular technique were less well practised in Southmead. These were the newer techniques and both were unpopular with some operators. Subcuticular repair is technically more difficult than the interrupted approach; polyglycolic acid sutures have different handling properties (Trimbos & Klopper 1985; Rahman & Way 1972) and many operators in this trial found chromic catgut and silk easier in this respect. Only further trials in other settings can resolve which of these two explanations is correct.

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The choice of suture materials and techniques for repair of perineal trauma: an overview of the evidence from controlled trials

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Summary. A systematic review of the 14 relevant controlled trials was conducted because there is no agreement about the choice of material and technique for repair of perineal trauma sustained during childbirth. Derivatives of polyglycolic acid (marketed as Dexon and Vicryl) appear to be the absorbable material of choice for both deep and skin closure. Compared with catgut their use is associated with about a 40% reduction in short-term pain and need for analgesia. The main drawback is that some material often needs removal during the puerperium. Glycerol-impregnated catgut is ruled out because of its link with long-term dyspareunia. Compared with the non-absorbable materials (silk and nylon) polyglycolic acid skin sutures were associated with less short-term perineal pain, and had no clear disadvantages. Continuous, subcuticular stitching appears preferable to interrupted, transcutaneous suturing, particularly in terms of perineal pain in the early puerperium.

There is no consensus as to which materials and which technique of skin closure should be used for repair of perineal trauma sustained during childbirth (Grant 1986). To help make an informed choice, a formal overview (Yusuf *et al.* 1985) of controlled trials of suture materials and suturing techniques was conducted. Three broad comparisons were made: (1) between absorbable suture materials when used throughout the repair; (2) between absorbable and non-absorbable materials removed during the puerperium, for perineal skin closure; and (3) between continuous, subcuticular, and interrupted transcutaneous sutures for perineal skin closure.

Materials and methods

Controlled trials of perineal suturing materials and techiques were identified from the Oxford Database of Perinatal Trials (Chalmers *et al.* 1986; Chalmers 1988). Reports are entered on to the database if the interventions being assessed have occurred during human pregnancy or within 28 days of delivery, and the allocation of the interventions has been decided either by formal randomization or by some other 'quasi-random' method such as alternation.

Fourteen studies were identified, including Mahomed *et al.* (1989); some reports incorporated more than one comparison. Details of the treatments compared are given in Tables 1–3.

Methodological quality

The extent to which the studies could have been distorted by bias was assessed using the approach described by Prendiville *et al.* (1988). The sealed envelope method was used for random allocation in five trials; the method of 'randomization' was not specified in a further four; and date of birth or alternation was used in

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Table 1. Description of trials comparing two absorbable materials used for all layers

Study	Entry criteria	First absorbable group (*n*)	Second absorbable group (*n*)
Tompkins & Lea (1972)	Episiotomy	PGA (25), subcuticular to skin	Chromic catgut (25), subcuticular to skin
Beard *et al.* (1974)	Mediolateral episiotomy, normal delivery	PGA (100). subcuticular to skin	Chromic catgut (100), subcuticular to skin
Livingstone *et al* (1974)	Mediolateral episiotomy, primigravidae, instrumental or normal delivery	PGA (50), interrupted to skin	Plain catgut (50), interrupted to skin
Rogers (1974)	Episiotomy—median and mediolateral	PGA (299), type of skin suture not stated	Chromic catgut (301), type of skin suture not stated
Banninger *et al* (1978)	Episiotomy, primigravidae, normal delivery	PGA (80), interrupted to skin	Chromic catgut (73), interrupted to skin
Roberts & McKay Hart (1983)	Mediolateral episiotomy, instrumental or normal delivery	PGA (88), interrupted to skin	Catgut (84), interrupted to skin
Mahomed *et al* (1989)	Perineal trauma requiring repair	PGA (275), interrupted and subcuticular to skin	Chromic catgut (263), interrupted and subcuticular to skin
Spencer *et al* (1986)	Perineal trauma requiring repair, normal delivery	Glycerol-impregnated catgut (Softgut) (377), interrupted and subcuticular to skin	Untreated chromic catgut (360), interrupted and subcuticular to skin

PGA, Polyglycolic acid

four. The method of allocation is not known for the study reported by Tompkins & Lea (1972) despite attempts to contact the authors, but this report does not include any relevant data and so does not contribute to the overview. Withdrawals after trial entry were not common. Only eight studies incorporated longer-term follow-up, but in one of these (Banninger *et al.* 1978) only about one in three women was reassessed. In most reports it was impossible to judge whether any attempt had been made to minimize assessment (observer) bias, although in five there was an indication that this was recognized as a potential problem. In the overviews pre-

Table 2. Description of trials comparing absorbable with non-absorbable skin sutures for repair of perineal trauma

Study	Entry characteristics	Absorbable group (*n*)	Non-absorbable group (*n*)
Polyglycolic acid vs silk			
Hansen *et al* (1975)	Mediolateral episiotomy	Interrupted PGA to skin (136), PGA to deeper tissues	Interrupted silk to skin (145), chromic catgut to deeper tissues
Bendsen & Madsen (1980)	Episiotomy	Subcuticular PGA to skin (108), PGA to deeper tissues	Interrupted silk to skin (103), PGA to deeper tissues
Buchan & Nicholls (1980)	Mediolateral episiotomy, primigravidae, normal delivery	Subcuticular PGA to skin (70), chromic catgut to deeper tissues	Interrupted silk to skin (70), chromic catgut to deeper tissues
Mahomed *et al* (1989)	Perineal trauma requiring repair following vaginal delivery	45% subcuticular, 55% interrupted, PGA to skin (535), 50% PGA and 50% chromic catgut to deeper tissues	Interrupted silk to skin (517), 50% PGA and 50% chromic catgut to deeper tissues
PGA vs nylon			
Isager-Sally *et al* (1986)	Mediolateral episiotomy	50% subcuticular (535) and 50% interrupted, PGA to skin, PGA to deeper tissues	Interrupted nylon to skin (267), plain catgut to deeper tissues
Catgut vs supramid			
Gaasemyr *et al* (1977)	Mediolateral episiotomy, normal delivery	Chromic catgut to skin (40), (? interrupted), chromic catgut to deeper tissues	Interrupted Supramid (60), chromic catgut to deeper tissues

PGA, Polyglycolic acid

Table 3. Description of trials comparing continuous with interrupted suturing techniques for closure of the perineal skin following perineal trauma

Study	Entry criteria	'Continuous' group (*n*)	'Interrupted' group (*n*)
Banninger *et al* (1978)	Episiotomy, primigravidae, normal delivery	Subcuticular PGA (80), PGA to deeper tissue	Interrupted PGA (80), PGA to deeper tissue
Detlefson *et al* (1980)	Mediolateral and median episiotomies	Subcuticular PGA (52), PGA to deeper tissue	Interrupted PGA (65), PGA to deeper tissue
Isager-Sally *et al.* (1986)	Mediolateral episiotomy	Subcuticular PGA (267), PGA to deeper tissue	Interrupted PGA (263), PGA to deeper tissue
Mahomed *et al.* (1989)	Perineal trauma requiring repair following vaginal delivery	Subcuticular (533), 50% chromic catgut, 50% PGA, similar materials to deeper tissues	Interrupted (524), 50% chromic catgut, 50% PGA, similar materials to deeper tissues

PGA, Polyglycolic acid.

sented below, the studies are ranked in order of methodological quality to allow an assessment of whether this has any systematic effect on the within-trial estimates of treatment differences.

Statistical methods

Information from similar trials has been analysed using the techniques described by Yusuf *et al.* (1985). Comparison between the two trial groups is expressed as a ratio of the odds (chances) of a particular outcome among women allocated to receive one treatment, with the odds (chances) of the same outcome amongst women in the other group, the odds ratio. In each individual trial the odds ratio may be exaggerated or underestimated because of the play of chance; the 95% confidence interval (CI) is a measure of this. But the sum of the differences derived from several independent trials, used in combination with the sum of the variances of the differences, provides a more precise estimate of the differential effect of the two treatments. These can be used to calculate a 'typical' odds ratio and CI.

Results

The choice of absorbable suture materials for perineal repair

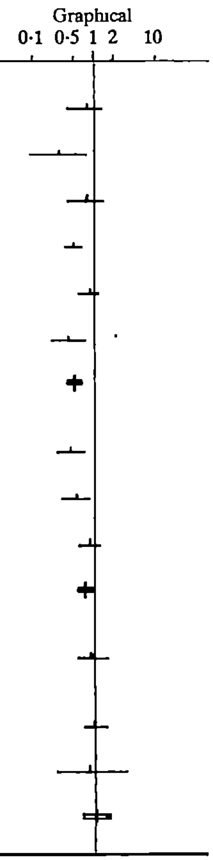
The absorbable materials most commonly used for perineal skin repair in England are polyglycolic acid (either the homopolymer, polyglycolide (Dexon, Davis & Geck Ltd) or the co-polymer with lactide, polyglactide (Vicryl, Ethicon Ltd) and chromic catgut (Grant 1986). One attraction of absorbable materials is that the same materials can be used for all layers. Seven controlled studies (Tompkins & Lea 1972; Beard *et al.* 1974; Livingstone *et al.* 1974; Rogers 1974; Banninger *et al.* 1978; Roberts & McKay Hart 1983; Mahomed *et al.* 1989) have compared polyglycolic acid (all polyglycolide—'Dexon') with catgut (mostly chromic catgut) when used for all layers. A similar technique was used in each trial for the two groups. These trials are summarized in Table 1. In three trials interrupted skin sutures were used; in two trials continuous sutures were used; and in one trial half the sutures were interrupted and half continuous. Details of the suturing technique used in the seventh trial are not known.

Data for four principal measures of outcome—short-term perineal pain, short-term analgesia use, longer-term pain and dyspareunia—where available, have been considered. Tompkins & Lea (1972) who provide no data report less pain in the early puerperium associated with polyglycolic acid sutures. This is consistent with all the other published trials (Table 4*a*), which suggest that the odds of pain are nearly halved. The results for analgesia use during the immediate puerperium also suggest that women whose perineal trauma was repaired with polyglycolic sutures suffer less pain during the early puerperium than those repaired with either chromic or plain catgut (Table 4*b*).

Unfortunately only one (Mahomed *et al.* 1989) of the seven trials, which together suggest such clear-cut short-term advantages for polyglycolic sutures, includes adequate follow-up after discharge from hospital. In this trial both perineal pain (Table 4*c*) and dyspareunia (Table 4*d*) were equally common in the two groups 3 months after delivery. Only 46 (30%) of the 160 women in the trial conducted by Banninger *et al.* (1978) returned for reassessment 3 months after

Table 4. Comparison of polyglycolic acid (PGA) with catgut for perineal repair

Study	PGA *n*	PGA (%)	Catgut *n*	Catgut (%)	Odds ratio and 95% CI Numerical
(a) Short-term pain					
Roberts & McKay Hart (1983)	23/88	(26·14)	29/84	(34·52)	0·67 (0·35–1·29)
Livingstone *et al* (1974)	39/50	(78·00)	48/50	(96·00)	0·21 (0·06–0·66)
Beard *et al* (1974)	64/100	(64·00)	72/100	(72·00)	0·69 (0·38–1·25)
Rogers (1974)	155/299	(51·84)	225/301	(74·75)	0·37 (0·27–0·52)
Mahomed *et al* (1989)	130/270	(48·15)	134/253	(52·96)	0·83 (0·59–1·16)
Banninger *et al* (1978)	14/80	(17·50)	29/73	(39·73)	0·34 (0·17–0·68)
Typical odds ratio					0·54 (0·44–0·65)
(b) Short-term analgesia use					
Roberts & McKay Hart (1983)	32/88	(36·36)	49/84	(58·33)	0·42 (0·23–0·76)
Beard *et al* (1974)	21/100	(21·00)	36/100	(36·00)	0·48 (0·26–0·89)
Mahomed *et al.* (1989)	129/270	(47·78)	135/254	(53·15)	0·81 (0·57–1·14)
Typical odds ratio					0·64 (0·49–0·84)
(c) Long-term pain					
Mahomed *et al* (1989)	25/232	(10·78)	28/233	(12·02)	0·88 (0·50–1·57)
(d) Dyspareunia					
Mahomed *et al* (1989)	56/227	(24·67)	56/228	(24·56)	1·01 (0·66–1·54)
Banninger *et al.* (1978)	4/25	(16·00)	4/21	(19·05)	0·81 (0·18–3·69)
Typical odds ratio					0·99 (0·66–1·49)



delivery: four women in each group complained of persistent dyspareunia.

A striking finding reported by Mahomed *et al.* (1989) was that the removal of some suture material was far more common in the polyglycolic acid group. This was particularly marked in the first 10 days (33% *vs* 12%), but persisted up to 3 months after delivery (41% *vs* 21%). The commonest reasons given were 'irritation' and 'tightness'. Two women reported by Banninger *et al.* (1978) and three reported by Mahomed *et al.* (1989) were judged to require resuturing and these were all in the catgut groups. This is consistent with Livingstone *et al.* (1974) who found only one woman with major dehiscence in the polyglycolic acid group, compared with three in the catgut group.

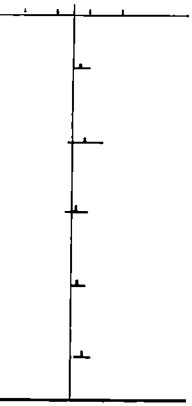
The only other published trial of two absorbable materials (Spencer *et al.* 1986) compared glycerol-impregnated catgut ('Softgut', soft catgut—Braun, Davis & Geck Ltd) with untreated chromic catgut, both materials being used for all layers (Table 1). Glycerol-impregnated catgut was associated with statistically significantly more pain 10 days after delivery and an increased prevalence of dyspareunia 3 months postpartum (Table 5). A further follow-up 3 years after delivery has recently been completed (Grant *et al.* 1989). The increased prevalence of dyspareunia persisted, reports of pain during sexual intercourse being nearly twice as common in the glycerol-impregnated catgut group (Table 5). Another finding was that untreated catgut stitches were much more likely to be removed in the puerperium than were glycerol-treated sutures (11·5% *vs* 2·4% in the first 10 days; and 16·4% *vs* 6·9% in the first 3 months).

Perineal skin closure: comparisons of 'absorbable' materials with non-absorbable materials removed during the puerperium

Six controlled studies have compared absorbable with non-absorbable skin sutures (Table 2).

Table 5. Comparison of glycerol-impregnated catgut (GIC) with untreated chromic catgut (UC) for perineal repair

Study	GIC *n*	GIC (%)	UC *n*	UC (%)	Odds ratio and 95% CI: Numerical	Odds ratio and 95% CI: Graphical 0·1 0·5 1 2 10
(a) Perineal pain at 10 days						
Spencer *et al* (1986)	107/335	(31·94)	75/321	(23·36)	1·53 (1·09–2·16)	
(b) Oral analgesia at 10 days						
Spencer *et al* (1986)	12/335	(3·58)	6/321	(1·87)	1·90 (0·74–4·84)	
(c) Perineal pain at 3 months						
Spencer *et al* (1986)	30/339	(8·85)	24/332	(7·23)	1·24 (0·71–2·17)	
(d) Dyspareunia at 3 months						
Spencer *et al* (1986)	78/300	(26·00)	57/292	(19·52)	1·44 (0·98–2·12)	
(e) Dyspareunia at 3 years						
Grant *et al* (1989)	51/263	(19·39)	29/253	(11·46)	1·83 (1·14–2·95)	



Four (Hansen *et al.* 1975; Bendsen & Madsen 1980; Buchan & Nicholls 1980; Mahomed *et al.* 1989) compared polyglycolic acid (Dexon) sutures with interrupted silk. In two of these the polyglycolic acid sutures were subcuticular, in one interrupted, and in the fourth 50% interrupted and 50% continuous. All except Hansen *et al.* (1975) used similar materials for the deeper tissues in the two trial groups. In general, the groups repaired with polyglycolic acid sutures left to dissolve had less pain (Table 6*a*) and used less analgesia in the first 5 days after delivery. Buchan & Nicholls (1980) report significantly less perineal discomfort associated with subcuticular polyglycolic acid in the immediate postpartum period, but data are not available for inclusion in the formal overview.

The situation in respect of longer-term morbidity is less clear. Buchan & Nicholls (1980) reported more long-term pain and dyspareunia in the polyglycolic acid group, but again they do not provide the data in a form which would allow them to be incorporated with those from the other trials. The results of the other trials tend to support this but, taken on their own, provide no clear evidence of a difference in long-term pain (Table 6*b*) or dyspareunia (Table 6*c*).

The other two trials which compared absorbable with non-absorbable skin sutures compared polyglycolic acid with the polyamide nylon (Isager-Sally *et al.* 1986) and chromic catgut with the polyamide Supramid (Gaasemyr *et al.* 1977). Their results are consistent with the polyglycolic acid *vs* silk trials: less pain and analgesia in the polyglycolic acid group in the short term, no clear difference in the longer term (Table 6).

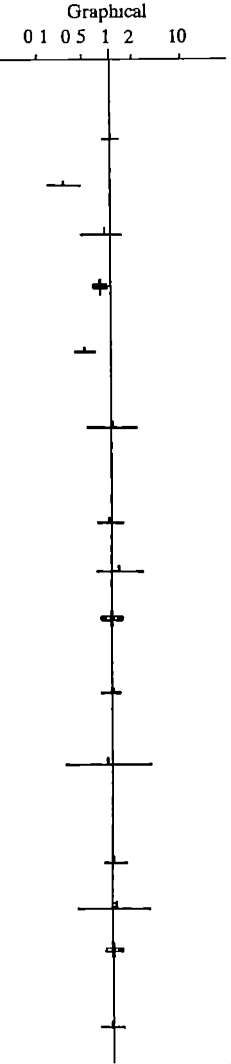
Subcuticular or interrupted sutures for perineal skin closure?

Four controlled studies (Banninger *et al.* 1978; Detlefson *et al.* 1980; Isager-Sally *et al.* 1986; Mahomed *et al.* 1989) have compared continuous subcuticular with interrupted transcutaneous suturing techniques for closure of the perineal skin (Table 3). All four trials used similar materials and techniques for repair of the deeper tissues in their two trial groups. In the first three, polyglycolic acid (Dexon) sutures were used throughout. The balanced factorial design used by Mahomed *et al.* (1989) resulted in approximately 50% being repaired with polyglycolic acid and 50% with chromic catgut in each trial group.

The three earlier (but smaller) trials (Banninger *et al.* 1978; Detlefson *et al.* 1980; Isager-Sally *et al.* 1986) all suggested that the continuous, subcuticular technique was associated with fewer short-term problems. Although women in the trial by Mahomed *et al.* (1989) reported somewhat more pain on the second postpartum day after subcuticular repair, by the 10th day this trend was reversed. Thus the overview strongly suggests that continuous, subcuticular sutures are associated with less pain than interrupted transcutaneous sutures in the immediate postpartum period (Table 7*a*). The three trials which provided the relevant data are also consistent in

Table 6. Comparison of absorbable with non-absorbable suture materials for perineal skin closure

Study	Absorbable *n*	Absorbable (%)	Non-absorbable *n*	Non-absorbable (%)	Odds ratio and 95% CI: Numerical
(a) Short-term perineal pain					
PGA *vs* silk					
Mahomed *et al* (1989)	142/450	(31·56)	140/444	(31 53)	1·00 (0·76–1·33)
Bendsen & Madsen (1980)	24/108	(22 22)	62/103	(60·19)	0·21 (0·12–0·36)
Hansen *et al* (1975)	16/136	(11·76)	22/145	(15·17)	0 75 (0·38–1 48)
Typical odds ratio					0·72 (0 57–0 92)
PGA *vs* nylon					
Isager-Sally *et al.* (1986)	370/523	(70·75)	236/269	(87 73)	0 39 (0·28–0·55)
Chromic catgut *vs* supramid					
Gaasemyr *et al* (1977)	29/40	(72·50)	43/60	(71·67)	1·04 (0·43–2·53)
(b) Long-term perineal pain					
PGA *vs* silk					
Mahomed *et al.* (1989)	54/458	(11·79)	54/450	(12 00)	0·98 (0·66–1·46)
Hansen *et al* (1975)	15/124	(12·10)	12/135	(8·89)	1 41 (0·64–3 12)
Typical odds ratio					1·05 (0·74–1 51)
PGA *vs* nylon					
Isager-Sally *et al* (1986)	173/515	(33 59)	87/266	(32·71)	1·04 (0 76–1 42)
Chromic catgut *vs* supramid					
Gaasemyr *et al.* (1977)	3/40	(7 50)	5/60	(8·33)	0·89 (0·21–3·88)
(c) Dyspareunia					
PGA *vs* silk					
Mahomed *et al.* (1989)	105/400	(26 25)	94/379	(24·80)	1·08 (0·78–1·49)
Hansen *et al.* (1975)	5/124	(4·03)	5/135	(3·70)	1·09 (0 31–3·86)
Typical odds ratio					1·08 (0·79–1·48)
PGA *vs* nylon					
Isager-Sally *et al* (1986)	103/515	(20·00)	57/266	(21 43)	0·92 (0·64–1·32)



PGA, Polyglycolic acid

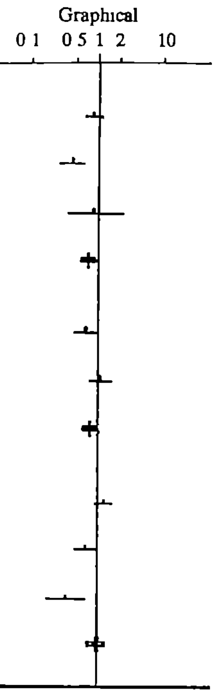
that women repaired with a subcuticular suture reported less analgesic use in the puerperium (data not suitable for quantitative synthesis). Both Detlefson *et al.* (1980) and Isager-Sally *et al.* (1986) reported less long-term pain and dyspareunia associated with subcuticular suturing. Mohamed *et al.* (1989) found little, if any, difference in pain at 3 months postpartum, but somewhat more dyspareunia in the continuous suture group. Combining the results from these three trials suggests that there are no substantial differences between the two techniques in respect of long-term pain (Table 7*b* and *c*). The need for resuturing was reported in two of the studies. This was necessary for three women in each trial group reported by Mahomed *et al.* (1989) and for no women in the trial reported by Banninger *et al.* (1978).

Discussion

The evidence presented is likely to provide the least biased estimates currently available of the differential effects of suture materials and sutur-

Table 7. Effect of continuous *vs* interrupted sutures for perineal repair

Study	Continuous *n*	Continuous (%)	Interrupted *n*	Interrupted (%)	Odds ratio and 95% CI Numerical
(a) Short-term pain					
Mahomed *et al.* (1989)	130/447	(29·08)	148/461	(32·10)	0·87 (0·65–1·15)
Isager-Sally *et al.* (1986)	24/262	(9·16)	60/261	(22·99)	0·36 (0·23–0·57)
Banninger *et al* (1978)	7/80	(8·75)	8/80	(10·00)	0·86 (0·30–2·49)
Typical odds ratio					0·69 (0·55–0·88)
(b) Long-term pain					
Isager-Sally *et al.* (1986)	77/265	(29·06)	96/250	(38·40)	0·66 (0·46–0·95)
Mahomed *et al.* (1989)	57/465	(12·26)	51/451	(11·31)	1·10 (0·73–1·64)
Typical odds ratio					0·83 (0·63–1·09)
(c) Dyspareunia					
Mahomed *et al.* (1989)	116/459	(25·27)	94/443	(21·22)	1·25 (0·92–1·71)
Isager-Sally *et al.* (1986)	45/265	(16·98)	58/250	(23·20)	0·68 (0·44–1·04)
Detlefsen *et al* (1980)	20/52	(38·46)	44/65	(67·69)	0·31 (0·15–0·64)
Typical odds ratio					0·90 (0·71–1·14)



ing techniques for perineal repair following childbirth. Nevertheless, better precautions could have been taken against selection bias introduced by insecure random allocation or post-randomization withdrawals, and assessment (observer) bias (Chalmers 1989). Bias may also have resulted from selective publication of those trials which showed significant differences between the policies (Hetherington *et al.* 1989). Unfortunately, the extent of these possible biases is impossible to assess with the information currently available. Another methodological deficiency is that longer-term follow-up was only included in 8 of the 14 studies.

Generally speaking, however, the overviews give a consistent picture. Of the commonly used absorbable materials, polyglycolic acid appears to be the material of choice for deep and skin closure. On the basis of currently available evidence, glycerol-impregnated chromic catgut (Softgut) should not be used because of its association with perineal pain and long-term dyspareunia (Table 5). Polyglycolic acid appears preferable to untreated chromic catgut in the short term, and in terms of dehiscence. Otherwise, there is no clear difference in the long term (Table 4). But the very frequent need (40%) to remove polyglycolic acid material in the puerperium because of 'irritation' indicates either that this material is not ideal or that the stitches were tied too tightly.

Polyglycolic acid sutures were associated with less pain in the immediate puerperium than both of the non-absorbable materials, silk and nylon (Table 6). No clear differences were observed in the longer term. Buchan & Nicholls (1980) did not provide data in a form which could be incorporated into the overview, but they report significantly more dyspareunia associated with polyglycolic acid; judgement should, therefore, be reserved on this issue. No trial compared two non-absorbable materials; but, if a non-absorbable material is chosen for skin closure, evidence from Mahomed *et al.* (1989) suggests that polyglycolic acid should be the absorbable material used for repair of the deeper tissues.

Polyglycolic acid sutures cause minimal tissue reaction (Craig *et al.* 1975), and this contrasts with chromic catgut and silk, both of which elicit a polymorphonuclear reaction (Lawrie *et al.* 1959; Capperauld 1975). This is the most likely explanation for decreased pain in the immediate postpartum period associated with the use of polyglycolic acid sutures. Another explanation may relate to differences in the tightness of the stitches rather than differences in the materials *per se.* All seven trials assessed polyglycolide (Dexon). The knotting properties of polyglycolide and chromic catgut are different (Trimbos & Klopper 1985). Initial throws of polyglycolide sutures hold better, double throws are needed with catgut but the stitch can be tightened with the second throw; but these differences are less marked for the newer coated polyglycolide (Dexon plus, Davis & Geck Ltd) and the co-polymer with lactide polyglactide (Vicryl, Ethicon Ltd).

Glycerol-impregnated chromic catgut causes a polymorphonuclear reaction similar to chromic catgut (Stone *et al.* 1985). The reason for the association of glycerol-impregnated catgut with long-term dyspareunia is uncertain. It could reflect a later tissue response with increased fibrosis either due to the glycerol or due to differences in the catgut (Grant *et al.* 1989). Of the non-absorbable materials, polyamides would be expected to cause less short-term pain than silk because they cause less tissue reaction and pass easily through the tissues; but handling and knotting of polyamides is less easy, they tend to be stiff and have a 'memory', and they thus require three or four throws in a knot. The handling properties of silk, on the other hand, are probably the best of all suture materials and silk knots easily and securely (Capperauld 1975). These latter characteristics almost certainly explain the continuing popularity of silk for perineal repair (Grant 1986), despite its unsuitability in terms of increased discomfort.

A continuous, subcuticular stitch appears to be preferable to interrupted, transcutaneous sutures. The subcuticular technique was associated with less short-term pain and there was no clear difference in the longer term (Table 7). This approach is particularly suitable for the experienced operator, but the easier, interrupted technique may well cause fewer problems in the hands of the inexperienced or novice operator (Grant 1989), or for jagged tears.

In summary, on the basis of currently available research evidence, polyglycolic acid sutures (Dexon or Vicryl) should be chosen for repair of both the deep layers and perineal skin, with a continuous, subcuticular suture to appose the skin. Questions still remain about the long-term implications of this policy. This still needs further research but, generally speaking, the available evidence is reassuring. The very frequent need to remove polyglycolic acid material in the puerperium, however, indicates that this policy is not ideal. A logical development would seem to be a continuous, subcuticular, synthetic, skin suture which could be removed easily in the early puerperium. Such a development should be rigorously evaluated before introduction into clinical practice.

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Alternative positions in the second stage of labour: a randomized controlled trial

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Summary. A controlled clinical trial involving 151 primigravidae and 18 midwives assessed the acceptability and outcome of second-stage labour in upright positions. Women who had no specific antenatal preparation and preferences regarding labour positions were managed either conventionally (semi-recumbent and lateral), or encouraged to adopt upright positions (squatting, kneeling, sitting or standing) according to individual preference. Of the women allocated to the upright position 74% completed the second stage upright, with kneeling being the most favoured position, but squatting was, despite all assistance, too difficult to maintain. Adoption of upright positions resulted in a higher rate of intact perineums. There was a clinically apparent reduction of forceps deliveries in the upright group which influenced midwives' attitudes. Moving the parturient from recumbent to upright positions was often perceived to be beneficial when there was slow progress. Estimated blood loss was similar in the two groups, as was the condition of the newborn (Apgar score and umbilical artery pH). Alternative positions in the second stage of labour, in particular kneeling, are achievable even without specific birth aids and antenatal preparation. They appear safe, acceptable to most parturients and their midwives, and are easily integrated into modern labour ward practice; they may have clinical advantages which need further investigation.

A cross-cultural and historical look at birth practices shows that a variety of labouring positions were adopted which, however, were rarely recumbent (Engelmann 1882; Witkowski 1887; Jarcho 1934; Naroll *et al* 1961; Jordan 1983), and that despite existing customs and conventions regulating childbirth, women were usually able to choose and vary their posture during labour (Engelmann 1882). Clarke (1891) observed that postural change can improve the efficiency of labour, and Dunn (1976) suggested that the spontaneous striving by the parturient to relieve discomfort and pain could be guiding her to find the most advantageous positions.

During the last 300 years, medical opinion has favoured a shift to recumbent positions but this was implemented without verifying its appropriateness (Dundes 1987). Several physiological advantages have been claimed for non-recumbent labour: (i) gravity; (ii) lessened risk of aorto-caval compression (Scott & Kerr 1963; Humphrey *et al.* 1974); (iii) improved alignment of the fetus for passage through the pelvis ('drive

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angle') (Gold 1950); (iv) stronger and more efficient uterine contractions (Caldeyro-Barcia *et al.* 1960; Mendez-Bauer *et al.* 1975); and (v) radiological evidence of larger antero-posterior (Borrel & Fernstrom 1957) and transverse (Russell 1969) pelvic outlet diameters, resulting in an increase in the total outlet area in squatting and kneeling positions (Russell 1982).

Clinical trials on position in the first stage of labour have been inconclusive. Two studies (Diaz *et al.* 1976; Flynn *et al.* 1978) suggested advantages of ambulation in early labour over lying in bed, but this was not substantiated by other reports (McManus & Calder 1978; Williams *et al.* 1980).

The only published controlled trials in the second stage, which compare upright with conventional positions, involve birth chairs (Stewart *et al.* 1983; Hemminki *et al.* 1986; Turner *et al.* 1986; Stewart & Spiby 1989). Although birth chairs were preferred by some women, no advantages were found as regards length of second stage, rate of forceps delivery, or perineal trauma, and birth chairs have been associated with higher rates of postpartum haemorrhage (Turner *et al.* 1986; Stewart & Spiby 1989).

As far as we know, no controlled study has looked at the feasibility of alternative upright positions in the absence of specific birthing aids such as chairs. We designed an exploratory trial in which upright positions could be chosen in the second stage according to individual preference and comfort, and the outcome was compared with that in a control group which was managed semi-recumbent. The main endpoints were rate of operative delivery, length of second stage, perineal trauma, blood loss and condition of the newborn.

Patients and methods

The protocol was approved by the hospital ethics committee. All women in their first term pregnancy admitted in spontaneous or induced labour were entered into a register and allocated either to group A ('active', upright) or group B ('bed', recumbent), according to whether the last numeral of their hospital number and the calendar date of their admission to the labour ward added up to an even or odd number.

Only singleton pregnancies with cephalic presentation, at 37–42 weeks gestation, with maternal age between 16 and 35 years and no known high-risk factors, were included in the trial. Further exclusions occurred if the women had a decided preference of labour positions, elected to have an epidural, were managed by a midwife not participating in the study, or had an elective or emergency section in the first stage

Table 1 lists the primary reason for exclusion of 123 of the total of 274 women who were admitted during the trial period. Of the remaining 151 women, 73 were randomized into the upright group A and 78 into the recumbent group B. The two groups were well matched (Table 2).

In group A 'upright' second-stage positions were defined as squatting, kneeling, sitting upright (<30° from the vertical), or standing. Consent was sought by the attending midwife

Table 1. Primary reason for exclusion of 123 of 274 women admitted to the study

Reason for exclusion	Allocated labour position	
	Upright	Recumbent
Maternal factors (age, obesity)	3	2
High-risk pregnancy or antenatal complications	13	11
Preterm labour	3	5
Breech (vaginal delivery)	2	4
Caesarean section		
Elective	6	6
Emergency (all in first stage)	5	3
Epidural analgesia	10	11
Late admission or rapid progress	4	2
Midwife not participating in study	12	15
Prior patient preference about labour positions	2	4
Total	60	63

Table 2. Characteristics of the two groups

	Allocated labour position	
	Upright (n=73)	Recumbent (n=78)
Age (years)	24·5 (4·4)	24·6 (4·3)
Height (cm)	162·3 (6·2)	163·6 (6·1)
Infant birthweight (g)	3280 (383)	3340 (452)

Results are mean (SD) values.

soon after admission, and was given by all but one woman who in any case was not suitable for inclusion as she was already in advanced labour. Postural options were discussed, and during the second stage the woman was helped to adopt her chosen position(s), but could at any time she wished opt out and continue in a conventional recumbent position. Arbitrarily, the criterion for fulfilling allocation to the upright group was that at least one-third of the active, bearing-down phase was spent in one or more of the upright positions. The position for delivery itself was left to the discretion of the midwife and did not have to be upright to satisfy this criterion.

The women allocated to the recumbent group were managed in the conventional way which meant lying in bed recumbent, usually propped up to about 30° from the horizontal, or on the side. A spontaneous wish during second stage to adopt an upright position was honoured.

First-stage positions were not controlled, and patients were usually left to ambulate, sit up, or lie in bed as they wished. Both first and second stages were spent in the same delivery room. All deliveries, including those squatting, sitting and kneeling, were conducted on height-adjustable delivery beds.

Eighteen midwives, all fully trained staff, agreed to participate and conduct the second stage of each labour according to the random allocation protocol. Most midwives had a little previous experience with upright positions, usually due to an occasional patient request, but as a rule conducted labour in the conventional semi-recumbent or lateral positions, and had no stated preference towards either type of management. The deliveries of three other midwives, who were known to have a bias towards recumbent (2) or upright (1) management, were excluded from the analysis from the outset.

Analgesia with meptazinol (Meptid) and nitrous oxide (Entonox) was used to a similar extent in both groups. The rates for induction (by prostaglandin vaginal pessaries, or amniotomy and intravenous oxytocin) and augmentation were comparable in the two groups: 22 were induced (10 upright *vs* 12 recumbent) and 24 had oxytocin augmentation (10 upright *vs* 14 recumbent). The overall length of the first stage, timed from admission to labour ward, was similar (approx. 7 h). The average proportion of the first stage spent lying in bed, although not controlled in this study, was lower in the upright group (33%) than in the recumbent group (51%). This was probably because the women in the former group often spent some time trying out upright positions in preparation for the second stage.

Intravenous infusion tubing did not impede adoption of upright positions. Monitoring was usually in the form of an initial cardiotocographic recording followed by episodic tracings and intermittent listening with an ultrasound fetal heart detector after contractions. In some women, at the midwife's or doctor's discretion, continuous monitoring via external or fetal scalp electrode was used. The belts for external monitoring were sometimes felt to be uncomfortable in upright positions, but no patient had to be withdrawn from the study for inability to monitor the fetal heart rate.

Details of labour, outcome and the state of the newborn were recorded by the midwife managing the delivery. The active second stage was timed from when the maternal bearing-down efforts began; this was usually encouraged when the woman started to feel the urge to push. There was no arbitrary time limit for the duration of the second stage, and the usual indication for operative delivery was failure to progress, maternal exhaustion or fetal distress. Episiotomies were not done routinely but usually to avoid a potentially greater tear, or to expedite delivery if this was thought necessary, or electively for forceps deliveries. Blood loss was estimated visually. Apgar scores were assessed by the senior midwife attending the delivery, or the paediatrician if present, and umbilical artery blood was taken for blood gas analysis.

Statistical analysis used the χ^2-test on 2×2 contingency tables and the non-parametric Mann–Whitney *U*-test.

Results

Of the 73 women in the upright group, 54 (74%) completed the second stage as intended (Table

Table 3. Details of second-stage labour in the two groups

	Allocated position	
Variable	Upright (n=73) n (%)	Recumbent (n=78) n (%)
Number completing second stage as intended	54 (74)	63 (81)
Non-compliance with allocated position	19 (26)	15 (19)
Midwife initiated	4	9
Patient's preference	15	6
Predominant second-stage position		
Lateral	4 (5)	17 (22)
Semi-recumbent	15 (21)	46 (59)
Sitting	16 (22)	7 (9)
Kneeling	32 (44)	8 (10)
Squatting	4 (5)	—
Standing	2 (3)	—
Delivery position		
Lithotomy	7 (10)	14 (18)
Lateral	9 (12)	8 (10)
Semi-recumbent	31 (42)	45 (58)
Sitting	10 (14)	10 (13)
Kneeling	14 (19)	1 (1)
Squatting	2 (3)	—
Standing	—	—
Duration of pushing (min) Mean (SD)	48·8 (34·8)	47·1 (31·8)

3); they spent on average 83% of the bearing-down phase in an upright position. Of the other 19 women 15 were too tired, too sedated or too comfortable to move from a recumbent position, and in four women, progress or the fetal heart tracing were better in the lateral recumbent position and the doctor or midwife advised a change to this position. Of the 78 women allocated to the recumbent position 63 (81%) completed the second stage as intended; of the 15 women who changed to the upright position, six chose to do so and nine did so on the advice of the midwife in an attempt to improve slow progress. These midwife-initiated changes from 'recumbent' to 'upright' became increasingly frequent as the study progressed, with all but one instance occurring in the last 4 weeks. This constituted the reason for ending the trial after 3 months.

The most favoured upright position adopted was kneeling (Table 3). Women found it easy to maintain and particularly good for relieving backache, and midwives thought it gave good exposure for inspecting the perineum. In a typical kneeling posture, the parturient would face and lean on the fully raised head of the delivery bed. Squatting was also managed on the bed, but while many women tried it, most found the position difficult to maintain and tiring despite attempts by midwife and husband to support her from each side

Women in the upright group tended to be generally more 'mobile', adopting more positions for second stage: 31% tried three or more different positions, 45% tried two, and 24% stayed in the same position throughout. Of the women in the recumbent group only 5% tried three or more positions, 40% tried two, and 55% stayed in one position.

There was no significant difference in the duration of the bearing-down phase of the second stage between the two groups. However, the mean duration of perineal distension before delivery, taken from the time when the head stopped receding between contractions, was shorter if this time was spent kneeling (9·8 min, range 5–15) than if it was spent lying semi-recumbent (16·2 min, range 3–32) (Mann–Whitney test: $U = 110$, $P<0·01$).

Discussion

Although the labour ward staff had, on the whole, little experience with upright positions before this trial, they had no problems integrat-

Table 4. Outcome of labour by position in second stage

	Allocated position	
	Upright (n=73) n (%)	Recumbent (n=78) n (%)
Mode of delivery		
Spontaneous vaginal	66 (90)	66 (85)
Forceps or ventouse	7 (10)	12 (15)*
Caesarean section	—	—
Blood loss (ml) Mean (SD)	201 (131)	223 (157)
Number with blood loss >500 ml	4	8
State of perineum		
All patients		
Intact (incl. first-degree tear)	27 (37)	20 (26)**
Second-degree tear	24 (33)	26 (33)
Third-degree tear	—	2 (3)
Episiotomy	22 (30)	30 (38)
Women completing second stage as intended	(n=54)	(n=63)
Intact (incl. first-degree tear)	24 (44)	17 (27)***
Second-degree tear	19 (35)	19 (30)
Episiotomy	11 (20)	27 (43)
Condition of newborn		
Apgar score at 1 min		
10, 9	42	45
8, 7	26	23
<7	5	10
Apgar score at 5 min		
10, 9	70	73
8, 7	2	5
<7	1	—
Umbilical artery pH Mean (SD)	7·26 (0·04)	7·24 (0·04)

* NS; **NS; *** χ^2= 3·89; P <0·05.

ing this concept into the usual conduct of labour. Upright second stage was usually managed on the delivery bed, and the option given in the protocol to conduct the delivery itself in the accustomed semi-recumbent position was often used (Table 3) and was an important compromise for winning the midwives' co-operation.

We had to group lateral with dorsal recumbent positions in the recumbent group because lateral positions were already an integral part of routine management in our unit. However, there is evidence that lateral and upright positions may have some features in common, for example as regards the efficiency of uterine contractions (Roberts *et al.* 1983), and the ability of the sacrum to swing backwards. Ideally, lateral positions should be investigated as a separate category. The sitting position is also difficult to classify: although the trunk is upright, there are also similarities to the recumbent position in that a proportion of maternal weight is on the sacrum and coccyx, which can decrease the antero-posterior diameter (Borrel & Fernstrom 1957) and the area of the pelvic outlet (Russell 1982).

A particular problem with such an investigation is that the 'treatment' (adoption of alternative positions) is not standardized but includes the ability to choose between positions during labour; thus our study investigated 'upright' as well as 'mobile' second stage, and we saw that usually several different positions were adopted in the upright group. Such mobility and variation were often observed to be advantageous to progress. Standardization is more easily achieved in studies using birth chairs, but in the relatively fixed, static position of sitting in a birth chair there is less freedom to vary posture according to individual preference, and the parturient may lose out on the possible advantages of such 'mobility'.

The trial was ended when it became apparent that more midwives were changing recumbent patients to upright management, when second-stage progress was deemed unsatisfactory. Although there was no evidence of midwife bias in either direction during most of the study, towards the end a shift in attitudes became apparent in favour of trying alternative positions 'as a last resort', even though the woman had been allocated to the recumbent group. The nature of this study lent itself to this transgression against the protocol. the 'treatment' could be administered by simply suggesting that another position be adopted. According to a subsequent survey of the participating midwives, several forceps deliveries were thought to have been avoided in this way. Thus, although the difference in forceps rates between the two groups was not statistically significant, we suggest that it was clinically significant and influenced midwife attitudes in favour of upright management of second stage.

The lower rate of perineal damage in the women who actually spent the second stage upright (Table 4) was due to fewer episiotomies, while the occurrence of perineal tears remained comparable. This was not due to the adoption of different policies for perineal management, as in the study by Sleep *et al.* (1984), where a 'restrictive' policy for episiotomies was shown to be associated with more women having an intact perineum but also a significantly higher rate of perineal tears. Nor was it due to any difficulty in performing an episiotomy while the patient was upright, as the delivery itself was often conducted in a recumbent position. The difference was most marked for the subgroup who chose the kneeling posture: of 30 women, 17 (57%) had an intact perineum; but more labial lacerations were recorded after upright than recumbent second stage [15 of 54 (28%) *vs* 12 of 63 (19%)].

We suggest that this apparent 'perineum sparing' effect of upright second stage may be due to several factors. (1) The angular change of the pubic symphyseal joint during 'pelvic moulding', as demonstrated by Russell (1969), decreases the subpubic waste space and allows a more anterior passage of the presenting part, thereby putting less pressure on the perineum. This was best observed in kneeling positions, where the perineum often appeared relaxed and loosely applied. The increase in anterior lacerations in this subgroup would be consistent with this more anterior transit. (2) The observed shorter length of the perineal distension-to-delivery interval in a kneeling position may result in fewer episiotomies done for expediting delivery in cases of delay or perceived fetal distress (3) In contrast, in the dorsal semi-recumbent position the usual flexing up of the thighs causes a pulling forward of the perineum with tightening and narrowing of the vaginal orifice, an effect described previously (Leak 1955) This is further accentuated by the common practice of the parturients' legs being placed in a quasi-lithotomy position on the midwives' hips for something to push against. It may well be that the potential increase in the bony dimensions of the pelvis during hyperflexion/abduction of the hips (Russell 1982) occurs at the expense of increased posterior soft tissue trauma if recumbent and lithotomy positions are adopted.

Estimated blood loss was similar in both groups and there was no increase in postpartum haemorrhage in the upright group. This is in contrast to studies of upright posture in birth chairs (Stewart *et al.* 1983; Turner *et al.* 1986; Shannahan & Cottrell 1985; Stewart & Spiby 1989). We also did not observe significant perineal oedema and venous congestion in our upright group, as was described for birth chairs by Goodlin & Frederick (1983).

Being primigravidae, our subjects had no reference for comparison of the comfort of upright labour. However, it was apparent from their comments that in particular kneeling was found to be agreeable, and often relieved backache.

In our study the most favoured upright position was kneeling, in agreement with Naroll *et al.* (1961), who surveyed reports of birth practices from 76 non-European cultures. In our culture, Carlson *et al.* (1986) have shown that, left to themselves, primigravidae in second stage most frequently adopted a propped, semi-recumbent position, which they call 'sitting at 45°'; this was similar to the position most commonly adopted by the women in our control group. The status quo with regard to delivery positions is thus being maintained by maternal expectation as much as birth attendants' attitudes. However, there is also evidence that most women would like to be encouraged to adopt different birthing positions (Gupta & Lilford 1987) and the high compliance rate with trying alternatives in our study would support this view; the usual expectation of being recumbent during labour can be easily overcome by the attending midwife. This is despite the fact that a parturient usually does not even meet the midwife who will manage her delivery until she is admitted in established labour.

We can make no statement about squatting, except that this group of women found this posture difficult to maintain. We have since started, with a new group of midwives, a clinical trial to compare squatting with the semi-recumbent position, using a new obstetric aid, the 'Birth Cushion', which facilitates a supported squatting position on the delivery bed.

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Mode of delivery and future fertility

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Summary. A cohort of 22 948 women from a stable homogeneous population who gave birth for the first time between 1964 and 1983 were followed up prospectively. Analysis by mode of delivery showed that of those delivered by caesarean section 23·2% fewer had another pregnancy than those who had a spontaneous vaginal delivery. Women delivered by forceps were in an intermediate group. Miscarriage was more common in women who had been delivered by caesarean section. The relative infertility after caesarean section could not be accounted for by early sterilization, was not associated with maternal height or social status, and was only partly attributable to age.

Baird (1962) described relative infertility after caesarean section in Aberdeen women who gave birth for the first time between 1938 and 1947. At that time caesarean section was used very selectively, mainly for the more difficult labours. Fewer than 3% of women were involved, and it might have been the bad experience and the complications of labour, rather than the caesarean section itself which led to relative infertility. Due to major advances in surgical and anaesthetic techniques and in postoperative management, caesarean section in recent years is less of an ordeal and perhaps less traumatic physically than it was then. It is of interest, therefore, to consider whether the association of caesarean section with infertility pertains in more recent years.

In a case-controlled prospective cohort study with a 5-year follow-up from upstate New York, Zdeb *et al.* (1984) reported that women who had had a primary caesarean section had 11% fewer total subsequent pregnancies than the vaginal delivery group. It was estimated that there was little out-migration, thus few women were lost to follow-up. However, the data were extracted from birth certificates so neither sterilization nor early pregnancy failure could be considered.

Another study from the USA (Hemminki *et al.* 1985) did include data on early pregnancy outcomes and sterilization, but was based entirely on self-reported events in a national sample survey. Women whose first livebirth was by caesarean section were found to have 11% fewer total subsequent pregnancies and 12% fewer total births than a matched control group with a vaginal delivery; these differences were not statistically significant, and there was no difference in the proportion in the two groups who had no further pregnancies. However, these authors interpreted their data as showing a trend for reduced fertility after caesarean section, which the respondents reported as being partly voluntary and partly involuntary

The use of all subsequent births as the index of fertility is questionable, since in the USA most of the women who had a primary caesarean section would have had a repeat caesarean section in subsequent pregnancies and this in itself might have had an effect on later fertility.

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Table 1. Next fertility-related event by mode of delivery in first birth

Subsequent event	Mode of delivery in first birth							
	SVD		Inst.		CS		Total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Pregnancy	8888	(61·5)	3706	(57·0)	940	(47·2)	13 534	(59·0)
Sterilization	241	(1·7)	124	(1·9)	54	(2·7)	419	(1·8)
None	5319	(36·8)	2677	(41·1)	999	(50·1)	8995	(39·2)
Total	14 448	(100·0)	6507	(100·0)	1993	(100·0)	22 948	(100·0)

$\chi^2 = 166{\cdot}1$, d.f. $= 4$, $P<0{\cdot}0001$.

SVD, Spontaneous vaginal; Inst., instrumental; CS, caesarean section

Table 2. Proportion of women having a second pregnancy by year of first birth in 5-year cohorts and by mode of delivery in first birth

Year of first birth	Mode of delivery in first birth							
	SVD		Inst		CS		Total	
	n	(% with 2nd preg.)	*n*	(% with 2nd preg.)	*n*	(% with 2nd preg.)	*n*	(% with 2nd preg.)
1964–68	4542	(73·2)	1343	(69·2)	404	(55·9)	6290	(71·3)
1969–73	3919	(69·2)	1813	(65·9)	467	(58·7)	6198	(67·5)
1974–78	2775	(66·3)	1616	(62·9)	440	(55·9)	4832	(64·2)
1979–83	3212	(31·2)	1735	(32·5)	682	(28·3)	5629	(31·3)

SVD, Spontaneous vaginal; Inst., instrumental; CS, caesarean section.

Table 3. Outcome of second pregnancy by mode of delivery in first birth

Outcome of second pregnancy	Mode of delivery in first birth							
	SVD		Inst.		CS		Total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Birth	7745	(87·1)	3197	(86·2)	793	(84·4)	11 735	(87·3)
Induced abortion	471	(5·3)	203	(5·5)	53	(5·6)	727	(5·4)
Miscarriage	672	(7·6)	306	(8·3)	94	(10·0)[a,b]	1072	(7·9)[b]
Total	8888	(100·0)	3706	(100·0)	940	(100·0)	13 534	(100·0)

[a] $Z = 2{\cdot}61$, $P<0{\cdot}01$.

[b] $Z = 2{\cdot}29$, $P<0{\cdot}05$.

SVD, Spontaneous vaginal; Inst., instrumental; CS, caesarean section.

In Aberdeen, between 1964 and 1983 the rate of caesarean section rose from 6·3% to 13·1% which is comparable to the 10% rate in the study of Hemminki *et al.* (1985). It was decided to review fertility experience after different modes of delivery using the Aberdeen Maternity and Neonatal Data Bank (Samphier & Thompson 1981). Because the data bank covers all fertility-related events in a stable total population, the prospective cohort design could be used with recorded, as opposed to self-reported events. It was recognized that such a study could not address the question as to whether any infertility was voluntary or not, but it was hoped to find out

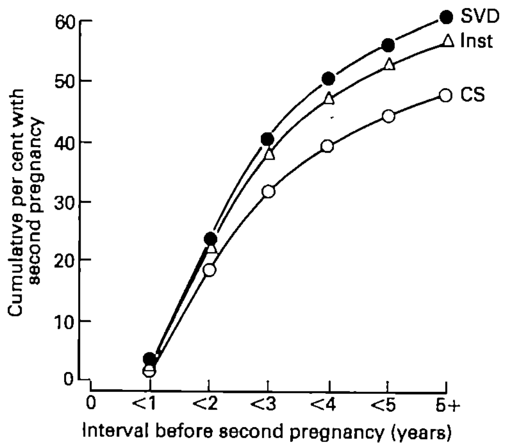

Fig. 1. Cumulative per cent of women with second pregnancy by mode of delivery in first birth and interval before second pregnancy.

whether there was a real difference in fertility experience after different modes of delivery.

Subjects and methods

During the period 1964–1983, 22 948 women having a first live singleton birth were identified from the data bank. Multiple births and stillbirths were not considered because it was felt that either of these events would influence future fertility much more strongly than mode of delivery was likely to do. Women with previous abortions were included. Fewer than 2% had more than one abortion, and it was not thought likely that this would influence future fertility significantly. Information on mode of delivery, age, height and social class at the time of the first birth was transferred to a SIR database together with details about the next fertility-related event (spontaneous or induced abortion, viable birth, sterilization or hysterectomy) in a follow-up period varying from 1 to 19 years. Information on vasectomy was not available.

The mode of delivery in the first birth was categorized as (a) spontaneous vaginal (SVD) including all cephalic deliveries and the 392 breech deliveries (breech deliveries were initially categorized separately, but were amalgamated with cephalic deliveries because in the analysis the results were similar); (b) instrumental (Inst.) (all forceps and ventouse deliveries); and (c) caesarean section (CS). The numbers, types and timing of subsequent events were identified. Only the first subsequent pregnancy or sterilization for each woman was included in the analysis. Differences in fertility experience were analysed by age, height, and social class.

Age was categorized in the usual 5-year groups; height in three groups: short ($\leqslant$1·545 m), medium (1·55–1·62 m) and tall ($\geqslant$1·625 m); and social status in four categories: three were based upon the husband's occupation (social class I–IIIa, IIIb and c, IV and V) and the fourth encompassed single, widowed, separated or divorced women.

Information on out-migration rates was obtained from the Grampian Health Board Information Services Division.

Results

Information about the out-migration rate for women in the reproductive age group was available only from 1980 onwards, and it was not practicable to link information on migration (obtained from the Primary Care Index) with mode of delivery. The out-migration rate (including deaths) was 1·6% in 1980, 2·4% in 1981, 2·6% in 1982 and 3·5% in 1983.

Overall, 39·2% of women had no further fertility-related event in the period studied, 1·8% were sterilized and 59·0% had another pregnancy (Table 1). The CS group had the lowest proportion of women with a further pregnancy and the highest proportion who were sterilized. The experience of women who had had an instrumental delivery was intermediate between that of women who had had a CS and those with SVD.

Study of the interval before the next pregnancy showed only a small increment in the rate of pregnancy after 5 years and results are shown with all pregnancies after 5 years amalgamated. The cumulative percentage of women having a second pregnancy set out by interval before the second pregnancy and by mode of first delivery (Fig. 1) shows that the divergence between the groups increases with the interval.

Looking at four 5-year birth cohorts by time of the first births (Table 2), caesarean section rates were 6·4%, 7·5%, 9·1% and 12% respectively. As expected, the proportion of women who had a second pregnancy was highest in the earliest cohort, who had the longest follow-up, and least in the latest cohort. For all cohorts, there were fewer women in the caesarean section group with a subsequent pregnancy than in the total group. The relative deficit of subsequent preg-

Table 4. Age distribution by mode of delivery in first birth

Age group (years)	Mode of delivery in first birth						Total	
	SVD		Inst.		CS			
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
15–19	3209	(22·2)	959	(14·7)	244	(12·2)	4412	(19·2)
20–24	7143	(49·2)	2736	(42·1)	714	(35·8)	10 593	(46·2)
25–29	3223	(23·3)	1984	(30·5)	575	(28·9)	5782	(25 2)
30–34	711	(4·9)	647	(9·9)	273	(13·7)	1631	(7·1)
35–39	123	(0·9)	150	(2·3)	136	(6·8)	409	(1·8)
40+	34	(0·2)	30	(0·5)	51	(2 6)	115	(0·5)
Missing	5	(0·03)	1	(0·02)	0	(-)	6	(0·03)
Total	14 448	(100·0)	6507	(100·0)	1993	(100·0)	22 948	(100·0)

$\chi^2 = 1267{\cdot}3$, d f. = 12, $P<0{\cdot}001$.

SVD, Spontaneous vaginal; Inst , instrumental; CS, caesarean section.

Table 5. Percentage of women having a second pregnancy by age and mode of delivery at first birth

Age group (years)	Mode of delivery at first birth			Total (% with 2nd preg.)
	SVD (% with 2nd preg)	Inst (% with 2nd preg.)	CS (% with 2nd preg.)	
15–19	69·4	64·0	62·7	67·8
20–24	63·5	63·2	53·9	62·8
25–29	55·6	52·7	45·2	53·6
30–34	46·1	43·1	41·0	44·1
35–39	35·0	33·3	22·1	30·1
40+	32·4	13·3	13·7	19·1

SVD, Spontaneous vaginal; Inst., instrumental, CS, caesarean section.

Table 6. Predicted percentage of women with a second pregnancy in the caesarean section (CS) group with the age distribution adjusted to that of all women

Age group (years)	Actual numbers in CS group	Numbers with age distribution adjusted to that in total group from Table 4	Actual percentage with second pregnancy from Table 5	Predicted number with second pregnancy if adjusted age groups have same fertility behaviour
15–19	244	383	62·7	240
20–24	714	921	53·9	497
25–29	575	502	45·2	227
30–34	273	141	41·0	58
35–39	136	36	22·1	8
40+	51	10	13·7	1
Total	1993	1993		1030 (51·7% of 1993)

nancies in the women originally delivered by caesarean section is largest in the earlier cohorts when the time for follow-up is greatest, and when the primary CS rates were lowest.

Table 3 shows that overall 5% of the second pregnancies ended in induced abortions, and this did not vary significantly by mode of delivery in the first birth. Miscarriage on the other hand was significantly more likely to occur after CS. Analysis of the outcome of second pregnancies by the interval between the first and second pregnancies showed no secular trend in the low rates of miscarriage and induced abortion, but the higher miscarriage rate in the group delivered by CS is confined to intervals of up to 2 years.

The age distribution at the time of the first birth by the mode of delivery (Table 4) makes it clear that women delivered by caesarean section are significantly older than average, and those delivered by forceps a little older than average. There is a clear gradient by age in the likelihood of having a second pregnancy (Table 5) from 67·8% in the teenage women, to only 19·1% in those aged ≥40 years. A similar gradient was apparent whatever the mode of delivery, but the relative deficit of births in the CS group was apparent in all age groups. In order to ascertain whether the different age distribution in the CS group explained the deficit in subsequent births, the age distribution in the CS group was adjusted to correspond with that in all births (Table 6). It was assumed that each adjusted 5-year age group would have the same percentage with a second pregnancy as the groups in the actual age distribution, and a predicted number with a second pregnancy arrived at. This totalled 1030 women out of 1993 with a second pregnancy (i.e. 51·7% compared to the actual value of 47·2%). The proportion of the total number of women who had a second pregnancy was 59%, so there is still a deficit in the CS group even after adjusting for age, but 38·1% of the deficit is accounted for by the difference in the age distribution.

The height distribution by mode of delivery is shown in Table 7. The proportion of short women in the CS group is twice that of those in the spontaneous vaginal delivery group and this is a significant difference. Overall, the proportion of women having a second pregnancy is lower in the tall women than in the short ones but within each height group there is a marked difference with mode of delivery, the deficit in the women delivered by CS being as great in the tall women as in the short (Table 8).

There is a small but significant social class gradient by mode of delivery (Table 9). Women in social classes I–IIIa are over-represented in

Table 7. Height distribution by mode of delivery in first birth

	Mode of delivery in first birth							
	SVD		Inst		CS		Total	
Height	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Short	2543	(17·6)	1340	(20·6)	703	(35·3)	4586	(20·0)
Medium	7776	(53·8)	3456	(53·1)	926	(46·5)	12 158	(53·0)
Tall	3691	(25·5)	1485	(22·8)	302	(15·2)	5478	(23·9)
Missing	438	(3·0)	226	(3·5)	62	(3·1)	726	(3·2)
Total	14 448	(100·0)	6507	(100·0)	1993	(100·0)	22 948	(100·0)

$\chi^2 = 379{\cdot}56$, d.f. = 6, $P<0{\cdot}001$

SVD, Spontaneous vaginal; Inst., instrumental; CS, caesarean section.

Table 8. Percentage of women with a second pregnancy by mode of delivery at first birth and height

	Mode of delivery at first birth			
Height	SVD (% with 2nd preg.)	Inst. (% with 2nd preg.)	CS (% with 2nd preg.)	Total (% with 2nd preg.)
Short	81·7	75·4	58·9	76·4
Medium	62·1	56·6	45·0	59·2
Tall	55·2	50·8	38·4	53·2

SVD, Spontaneous vaginal, Inst., instrumental; CS, caesarean section.

Table 9. Social status distribution by mode of delivery in first birth

Social status	Mode of delivery in first birth							
	SVD		Inst.		CS		Total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
I–IIIa	4335	(30·0)	2283	(35·1)	668	(33·5)	7286	(31·8)
III b + c	5073	(35·1)	2178	(33·5)	667	(33·5)	7918	(34·5)
IV + V	3488	(24·1)	1403	(21·6)	450	(22·6)	5341	(23·3)
Single etc	1115	(7·7)	453	(7·0)	125	(5·3)	1693	(7·4)
Missing	437	(3·0)	190	(2·9)	83	(4·2)	710	(3·1)
Total	14 448	(100·0)	6507	(100·0)	1993	(100·0)	22 948	(100·0)

$\chi^2 = 71{\cdot}43$, d.f. = 8, $P<0{\cdot}001$.

SVD, Spontaneous vaginal; Inst , instrumental; CS, caesarean section.

Table 10. Percentage of women with a second pregnancy by mode of delivery and social status at first birth

Social status	Mode of delivery at first birth			
	SVD (% with 2nd preg.)	Inst (% with 2nd preg.)	CS (% with 2nd preg.)	Total (% with 2nd preg.)
I–IIIa	56·8	54·6	43·9	54·9
III b + c	68·7	62·5	54·6	65·8
IV + V	68·4	61·9	50·9	65·2
Single etc	50·1	48·6	41·6	49·1

SVD, Spontaneous vaginal; Inst., instrumental, CS, caesarean section

the group delivered by CS or instrumental delivery. The likelihood of having a second pregnancy is considerably lower overall in social classes I–IIIa women and in single women (Table 10). Within each social class group, delivery by caesarean section is associated with a reduced proportion of women having a second pregnancy.

Discussion

CS or instrumental delivery might be associated with relative subsequent infertility by physical trauma, by deterring women from repeating the experience, or because of confounding factors such as the characteristics of women delivered in this way.

The extent of infertility following CS described here (18·9% fewer had another pregnancy compared with all first births, 23·2% fewer than after spontaneous vaginal deliveries) is greater than in the American reports quoted above. Indeed, neither American study found any difference in the proportion of women with no further pregnancy, but only in the average number of subsequent pregnancies, where only modest differences were found. We regard the proportion having at least one other pregnancy as the more appropriate measure, since the likelihood of third and fourth pregnancies occurring is at least as likely to be determined by the mode of delivery and outcome of the second pregnancy as those of the first.

The extent of infertility after instrumental delivery is considerably less than after CS (only 3·4% fewer had a second pregnancy than all women and 7·3% fewer than after spontaneous delivery). This was not considered at all in previous reports.

Analysis of subsequent pregnancy rates by the interval between pregnancies and by 5-year cohorts shows no sign that the deficit in births in the CS and instrumental delivery groups is due to postponement of the next pregnancy.

Although sterilization rates are slightly higher in the CS and instrumental delivery groups, this does not make a substantial contribution to the deficit in births. There is no variation to subsequent induced abortion rates by mode of delivery, but women previously delivered by CS had higher miscarriage rates. The fact that the increased rates are confined to the first 2 years suggests that pregnancy failure may be due to a combination of uterine damage at caesarean section and the short interval.

We examined whether the extent of infertility after caesarean section found in this population study is merely an association attributable to characteristics of the women concerned. Analysis by maternal height and social status shows no evidence of this, and increased maternal age explains only 38·1% of the deficit in pregnancies after caesarean section.

Whether the infertility is voluntary or largely involuntary (as found by Hemminki *et al.* (1985) in the USA) will be the subject of further research.

Acknowledgments

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Nausea and vomiting of early pregnancy and pregnancy outcome. An epidemiological study

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Summary. The association of nausea and vomiting in pregnancy with the outcome of pregnancy was investigated in a historical cohort of 903 women in Los Angeles, California, USA. Multivariable statistical methods were employed to control for the potential confounding effects of age, ethnicity, occupation, and anti-emetic use on pregnancy outcome. The analyses indicated that vomiting was associated with decreased risk of miscarriage (adjusted odds ratio 0·18, 95% CI 0·06 to 0·53); women with nausea but no vomiting had a miscarriage risk equal to that in the sample overall. Among the subsample of women with signs of threatened miscarriage, those who had experienced vomiting had a decreased risk of miscarriage (10·3% *vs* 31·7% in the subsample). No statistically significant association was observed between nausea and vomiting of pregnancy and other pregnancy outcomes (perinatal mortality, fetal anomalies, neonatal anthropometric measures).

Previous studies have indicated that nausea, vomiting, or both (morning sickness) occur in approximately 70% of all pregnancies (Brandes 1967; Midwinter 1971; Jarnfelt-Samsioe *et al.* 1983; Weigel & Weigel 1988). The reason for nausea and vomiting of pregnancy (NVP), including hyperemesis gravidarum, remains uncertain although rapidly increasing oestrogen levels during early gestation have been implicated (Jarnfelt-Samsioe *et al.* 1985; Bernstein *et al.* 1986; Weigel & Weigel 1988). The relation between NVP and the outcome of pregnancy continues to be an area of considerable controversy. A number of studies have reported that NVP is associated with favourable pregnancy outcomes such as decreased risk for miscarriage and perinatal death (Speert & Guttmacher 1954; Medalie 1957; Yerushalmy & Milkovich 1965; Brandes 1967, Tylden 1968; Milkovich & van den Berg 1976; Kullander & Kallen 1976; Jarnfelt-Samsioe *et al.* 1983; Klebanoff *et al.* 1985; Petitti 1986; Tierson *et al.* 1986), low infant birthweight (Brandes 1967; Tylden 1968; Little 1980; Tierson *et al.* 1986) and preterm birth (Brandes 1967; Tierson *et al.* 1986). It has been suggested also that women who continue to experience morning sickness during episodes of vaginal bleeding (threatened miscarriage) have decreased risk of subsequent miscarriage (Speert & Guttmacher 1954; Medalie 1957). Such evidence led Brandes (1967) to postulate that absence of symptoms of NVP may be a

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useful clinical marker for poor pregnancy outcome.

In contrast, other reports have suggested that NVP may be an indicator of unfavourable pregnancy outcome, e.g. increased risk for fetal anomalies (Kullander & Kallen 1976; Kricker *et al.* 1986) and low birthweight (Kricker *et al.* 1986) while others have found no relation between NVP and certain pregnancy outcomes, e.g. fetal anomalies (Fairweather 1968; Milkovich & van den Berg 1976; Klebanoff & Mills 1986), birthweight (Wolkind 1982; Klebanoff *et al.* 1985; Jarnfelt-Samsioe *et al.* 1983), length of gestation (Jarnfelt-Samsioe *et al.* 1983), and anthropometric indices of neonatal maturity (Kruse *et al.* 1975).

These diverse results make it difficult to ascertain the strength and generalizability of associations between NVP and pregnancy outcomes. Thus, the utility of NVP as a prognostic indicator is uncertain. Some of the variation among past studies may be due to true population differences, but it is also likely that a significant proportion of this variation is due to differences in methods of subject selection, sample size, and variation in the classification of pregnancy outcome measures. Some loss of power and precision in prediction may also be due to the dichotomization of symptoms (no symptoms *versus* nausea, vomiting *versus* no vomiting), whereas there are at least three levels (no symptoms, nausea only, nausea with vomiting) (Tierson *et al.* 1986; Weigel & Weigel 1988). Furthermore, some previous conclusions appear to be premature due to the failure to control for confounding variables (see Klebanoff *et al* 1985; Klebanoff & Mills 1986; Weigel & Weigel 1988) as well as the absence of hypothesis testing to support reported associations. In addition, in some studies the primary focus was the effect of anti-emetic drugs on pregnancy outcome (Yerushalmy & Milkovich 1965; Milkovich & van den Berg 1976; Kullander & Kallen 1976); thus the association of NVP with pregnancy outcome may be confounded by use of anti-emetics.

The major objective of our study was to investigate the association of NVP with pregnancy outcome in a large, diverse sample of pregnant women, employing multivariable statistical methods which control for the effects of confounding variables. Comparisons with results of previous studies are made here and in the subsequent paper (Weigel & Weigel 1989), to assess the generalizability of the association between NVP and pregnancy outcome.

Subjects and methods

Subjects eligible for inclusion in the study were all women with a singleton pregnancy who were delivered at the University of California, Los Angeles (UCLA) Hospital and Clinics, during a 1-year period between 1 April 1983 and 31 March 1984 (group 1). In addition, all women who miscarried before 21 weeks gestation and were treated at the UCLA Hospital and Clinics during the same period were eligible for study (group 2). Women eligible for the study were identified according to DRG (diagnostic related groups) classification, using the UCLA Hospital computerized database management system. Inclusion criteria for entry into the study were: (i) at least one prenatal visit at the UCLA clinics before 21 weeks gestation, and (ii) recording of presence or absence of nausea and vomiting on the medical records. Only the first pregnancy of an individual during the study period was included. Since NVP normally ceases by 20 weeks (Uddenberg *et al* 1971; Wolkind 1982; Alley 1984; Jarnfelt-Samsioe *et al* 1985), women lacking a prenatal visit before 21 weeks were excluded to minimize recall bias Uncertainty about the date of the last menstrual period was an additional criterion for exclusion. Women reporting nausea or vomiting or both only in conjunction with diarrhoea or fever were also excluded because of ambiguity of diagnosis.

Of the 2158 women potentially eligible for inclusion in group 1, 1285 were excluded for the following reasons: lost or missing maternal records (19), possibility of gastroenteritis (6), incomplete data on pregnancy outcome (3), first prenatal visit after 20 weeks or uncertain dates or both (1252), and absence of records about nausea and vomiting (5) This left 873 women in group 1 who met the criteria for inclusion These women had a mean age of 26·9 years (range 14–43), 58% were Hispanic and 26% were white, 51% were classified as housewives. For group 2, a total of 56 potentially eligible women with a diagnosis of miscarriage was identified and 30 of them met the criteria for inclusion in the study. These women had a mean age of 26·4 years (range 14–43); 43% were white and 32% were Hispanic, and 36% were classified as housewives. The differences in demographic characteristics between groups 1 and 2 were not statistically significant at the 0·05 level, although the ethnic and occupational differences were significant at the 0·10 level.

During intake, standard demographic information was recorded in the medical records. The women were asked about past reproductive history, signs and symptoms associated with the current pregnancy (e.g. date of last menstrual period, presence of vaginal bleeding, physical complaints), and use of alcohol, tobacco and other drugs (including anti-emetics). According to protocol, at the first visit each woman was asked specifically about the presence or absence of nausea and vomiting since the last menstrual period, and at subsequent visits they were asked about symptoms since the last visit.

Analytical methods

The women were divided into three ordered categories according to the most severe level of nausea and vomiting (0–2) they had experienced during the first 20 weeks gestation: level 0 (neither nausea nor vomiting); level 1 (nausea but no vomiting); and level 2 (vomiting in conjunction with nausea). The pregnancy outcome measures analysed were length of gestation, birthweight, body length at birth, head circumference, 1- and 5-min Apgar scores, placental weight, miscarriage (fetal death ≤20 weeks), threatened miscarriage (vaginal bleeding), perinatal death (fetal death >20 weeks, neonatal death), and severe fetal anomaly (of genetic or developmental origin). Length of gestation and birthweight were analysed both as interval and categorical variables. Gestation length was dichotomized to indicate preterm delivery (<37 weeks gestation) or its absence (≥37 weeks). Likewise, birthweight was dichotomized to indicate low birthweight (<2500 g) or its absence (≥2500 g) These divisions of continuous scales are warranted because they reflect standard obstetric classifications and identify apparent cut-off points for increased risk. However, reducing an interval scale to categories results in loss of available information, and therefore provides less precise estimates of association.

Using a one-way analysis of variance, we examined the simple associations of nausea and vomiting (grouped according to the three levels identified above) with the interval level pregnancy outcome measures of length of gestation, birthweight, body length, head circumference, and placental weight, and the ordinal level variables of 1-min and 5-min Apgar scores. The simple associations of levels of nausea and vomiting with the dichotomous pregnancy outcome categories of miscarriage, threatened miscarriage, perinatal mortality, fetal anomalies, preterm delivery, and low birthweight were assessed using 3×2 contingency table analyses, with the gamma statistic calculated to evaluate rank order correlation (Goodman & Kruskal 1954). In addition, 2×2 contingency table analyses were used, where NVP was alternatively dichotomized as nausea (with or without vomiting) *versus* no nausea, and vomiting *versus* no vomiting (with or without nausea), with odds ratios and 95% confidence intervals calculated to quantify risk for pregnancy outcomes (Miettinen 1976; Fleiss 1981). This dichotomization allows for easier comparison with previous studies, as well as indicating whether associations with pregnancy outcome are primarily due to vomiting, or whether nausea alone is a significant prognostic factor.

To test for the association of nausea and vomiting with the pregnancy outcomes independent of confounding variables, multivariable statistical analyses were conducted. In each case, the NVP category was analysed in conjunction with four potential confounders. Maternal age, white (*versus* non-white) ethnicity, and housewife (*versus* non-housewife) status were chosen as confounders because of their significant associations with NVP in a previous analysis of the same sample of women (Weigel & Weigel 1988), and their previously reported associations with pregnancy outcome (Niswander & Gordon 1972; Porter & Hook 1980; Naeye & Tafari 1984; Mamelle *et al.* 1984; Kieley *et al.* 1986). In addition, use of anti-emetic medication was included as a confounder, due to its suggested association with pregnancy outcome, especially fetal anomalies (Najouks 1953; Thalhammer 1953; Hohlbein 1961; Noack 1963; Yerushalmy & Milkovich 1965; Doring & Hossfeld 1976). Parity, pre-pregnancy weight, maternal body-mass index, interpregnancy interval, and marital status have also been shown to be associated with pregnancy outcome, but these factors were not included in the current analysis because the earlier study of the same sample showed no association with NVP (Weigel & Weigel 1988) Tobacco and alcohol consumption during pregnancy are known to have an effect on pregnancy outcome, as well as an association with NVP (Hook 1971, 1976; Little & Hook 1979, Little

Table 1. Association of nausea and vomiting of pregnancy (NVP) with pregnancy outcome measures

Pregnancy outcome	Overall		No NVP				Nausea only				Vomiting					
	n	Mean	*n*	Mean	(SEM)	Adj mean	*n*	Mean	(SEM)	Adj mean	*n*	Mean	(SEM)	Adj mean	ANOVA *P*	ANCOVA *P*
Gestation (weeks)	860	39·5	252	39·6	(0·17)	39·6	200	39·6	(0·16)	39·4	408	39·4	(0·13)	39·4	NS	NS
Birthweight (g)	861	3335	253	3333	(43·0)	3338	200	3413	(42·1)	3415	408	3299	(31·0)	3294	NS	NS
Placental weight (g)	705	623	207	613	(10·6)	613	161	624	(10·5)	624	337	630	(8·5)	629	NS	NS
Body length (cm)	839	50·0	249	49·9	(0·34)	49·8	196	50·5	(0·25)	50·5	394	49·9	(0·22)	49·9	NS	NS
Head circumference (cm)	665	34·5	205	34·7	(0·26)	34·7	151	34·5	(0·20)	34·5	309	34·5	(0·11)	34·5	NS	NS
Apgar score																
1 min	854	7·5	250	7·5	(0·11)	7·5	196	7·6	(0·13)	7·6	408	7·6	(0·08)	7·6	NS	NS
5 min	854	8·7	250	8·7	(0·07)	8·6	195	8·7	(0·07)	8·7	409	8·7	(0·05)	8·7	NS	NS

Adj mean. Mean after adjusting for covariates
ANOVA *P*. *P* value from analysis of variance
ANCOVA *P* *P* value from analysis of covariance
NS, Not significant

1980, Klebanoff *et al.* 1985). The previous study (Weigel & Weigel 1988) identified an association between alcohol and tobacco consumption before conception with a decreased risk for NVP, but this association essentially disappeared when other risk factors were taken into account. Unfortunately, for the current study, alcohol and tobacco consumption during pregnancy was not consistently recorded. Thus, this information was considered unreliable and these potentially influential variables were not included as confounders.

For the interval and ordinal level pregnancy outcome measures (length of gestation, birthweight, body length, head circumference, placental weight, 1- and 5-min Apgar scores), an analysis of covariance was conducted, with the confounding variables identified above as covariates. For the dichotomous pregnancy outcome variables, statistical control for confounders was achieved using a multiple logistic regression model. Adjusted odds ratios were calculated from these analyses (Afifi & Clark 1984) to assess risk of unfavourable outcome, adjusting for confounders. To prevent confounding effects of miscarriage on other pregnancy outcomes (e.g length of gestation, birthweight), miscarriages were included only in the analysis of threatened miscarriages and miscarriage outcomes.

Results

Nausea and vomiting during the first 20 weeks gestation occurred in 69% of our sample; 23% experienced nausea without vomiting, and 46% experienced vomiting in addition to nausea. Symptoms of NVP began typically at 4–6 weeks gestation, peaked in intensity between 8 and 12 weeks, and diminished thereafter until by 20 weeks relatively few women experienced either nausea or vomiting (Weigel 1985). Women with vomiting gained less weight during the first 20 weeks, mean weight gain· vomiting, 3·36 kg (SE 0·23); nausea only, 4·41 kg (SE 0·32); no symptoms, 4·73 kg (SE 0·23) (ANOVA $P<0·001$), although there were no significant differences in mean weight at the time of delivery: vomiting,

Table 2. Frequency and distribution of fetal outcome categories by nausea and vomiting in pregnancy (NVP)

Pregnancy outcome	Overall *n*	Overall (%)	No NVP *n*	No NVP (%)	Nausea only *n*	Nausea only (%)	Vomiting *n*	Vomiting (%)	Gamma
Miscarriage	32	(3·6)	20	(7·2)	8	(3·8)	4	(1·0)	−0·60***
Threatened miscarriage	101	(11·2)	37	(13·4)	25	(11·8)	39	(9·4)	−0·14
Perinatal mortality	9	(1·0)	3	(1·1)	2	(0·9)	4	(1·0)	−0·04
Fetal anomalies	10	(1·1)	3	(1·1)	4	(1·9)	3	(0·7)	−0·16
Preterm delivery	55	(6·1)	18	(6·5)	13	(6·2)	24	(5·8)	−0·07
Low birthweight	56	(6·2)	21	(7·6)	9	(4·3)	26	(6·3)	−0·08

Percentages are per cent of NVP class with pregnancy outcome
*** $P<0·001$.

Table 3. Odds ratios for association of nausea and vomiting (NVP) with pregnancy outcome categories

		2 × 2 contingency table analysis			Multiple logistic regression analysis		
Pregnancy outcome	NVP category	Crude odds ratio	*P*	(95% CI)	Adjusted odds ratio	*P*	(95% CI)
Miscarriage	Nausea	0·25	<0·001	(0·13 to 0·49)	0·32	0·002	(0·15 to 0·68)
	Vomiting	0·16	<0·001	(0·06 to 0·41)	0·18	0·001	(0·06 to 0·53)
Threatened miscarriage	Nausea	0·74	NS	(0·48 to 1·13)	0·82	NS	(0·51 to 1·31)
	Vomiting	0·71	NS	(0·47 to 1·09)	0·82	NS	(0·52 to 1·30)
Perinatal death	Nausea	0·88	NS	(0·22 to 3·57)	0·84	NS	(0·21 to 3·43)
	Vomiting	0·94	NS	(0·24 to 3·65)	0·93	NS	(0·24 to 3·55)
Fetal anomalies	Nausea	1·03	NS	(0·27 to 3·93)	0·89	NS	(0·22 to 3·57)
	Vomiting	0·50	NS	(0·13 to 1·90)	0·47	NS	(0·12 to 1·86)
Preterm delivery	Nausea	1·03	NS	(0·27 to 3·93)	0·91	NS	(0·49 to 1·67)
	Vomiting	0·50	NS	(0·13 to 1·90)	0·91	NS	(0·51 to 1·63)
Low birthweight	Nausea	0·88	NS	(0·22 to 3·57)	0·67	NS	(0·38 to 1·19)
	Vomiting	0·94	NS	(0·24 to 3·65)	0·96	NS	(0·55 to 1·67)

NS, Not significant.

73·4 kg (SE 0·73); nausea only, 74·1 kg (SE 1·1); no symptoms, 73·6 (SE 1·0) (ANOVA *P* = 0·37).

Table 1 indicates that none of the continuous pregnancy outcomes was statistically significantly associated with NVP. Several of the covariates were statistically significantly and independently associated with pregnancy outcome. With increasing maternal age, there was an increase in birthweight (*P*<0·05) and 5-min Apgar score (*P*<0·05). Housewives had higher infant birthweights (*P*<0·05) and placental weights (*P*<0·05). White women had babies with higher Apgar scores at 1 min (*P*<0·01) and 5 min (*P*<0·01). However, the nearly identical unadjusted and adjusted means indicate that the covariates did not affect the association of NVP with these pregnancy outcomes.

Table 2 shows the frequency of each dichotomous pregnancy outcome and the distribution of each variable across NVP levels. The gamma values revealed one highly significant (*P*<0·001) result, i.e. increased level of NVP was associated with decreased risk of miscarriage. No other association of NVP with pregnancy outcome was detected. Table 2 also reveals that the association with miscarriage was due primarily to increased risk for no NVP and decreased risk for vomiting (no NVP, 7·2% *vs* total sample, 3·6% *vs* vomiting, 1·0%), whereas miscarriage risk for nausea without vomiting (3·8%) was essentially equal to the rate in the total sample.

Table 3 shows the simple bivariate associations of each dichotomous pregnancy outcome with the dichotomizations of nausea and vomiting, respectively. Both nausea and vomiting were associated with decreased miscarriage risk only, with the association slightly stronger for vomiting. Table 3 also reports the results of the multiple logistic regression analysis. There were several significant independent associations of the confounders with the dichotomous pregnancy outcomes. Housewives had a decreased

Table 4. Relations between three levels of nausea and vomiting (NVP) and miscarriage after threatened miscarriage

	Level of nausea and vomiting			
Outcome after threatened miscarriage	No NVP *n* (%)	Nausea only *n* (%)	Vomiting *n* (%)	Overall *n* (%)
Miscarriage	20 (54·1)	8 (32·0)	4 (10·3)	32 (31·7)
No miscarriage	17 (45·9)	17 (68·0)	35 (89·7)	69 (68·3)

Gamma = −0·66, *P* <0·001

risk for threatened miscarriage ($P<0{\cdot}001$). Women in the 30–34-year age group had a decreased risk for miscarriage ($P<0{\cdot}05$), but an increased risk for fetal anomalies ($P<0{\cdot}05$). However, when the influence of the confounders was taken into account, it was apparent that both nausea and vomiting were still associated only with decreased risk of miscarriage, although the adjusted odds ratios revealed the associations were not as strong as indicated by the bivariate analyses.

Although the analyses shown in Tables 2 and 3 indicated no association of NVP with threatened miscarriage, Table 4 reveals that for the subsample of women with signs of threatened miscarriage, the rate of miscarriage decreased with increasing level of NVP (gamma = $-0{\cdot}66$; $P<0{\cdot}001$). Table 4 also indicates that, similar to the results for general association with miscarriage, decreased risk of miscarriage after threatened miscarriage was detected only in the vomiting group, whereas women with nausea had a miscarriage risk essentially equal to that in the total sample.

Discussion

'Morning sickness' is one of the most common complaints of women during the first 20 weeks gestation. The results of the current and previous studies indicate that mild to moderate (i.e. non-hyperemetic) nausea or vomiting or both is usual and a normal rather than a pathological characteristic of early gestation.

The results of the current study indicate that even when the effects of potential confounders are taken into account, NVP was still associated only with decreased miscarriage risk. This suggests that previous studies identifying a decreased risk of miscarriage with NVP, without taking potential confounders into account (Speert & Guttmacher 1954; Medalie 1957; Yerushalmy & Milkovich 1965; Brandes 1967; Kullander & Kallen 1976; Jarnfelt-Samsioe *et al.* 1983), inferred correctly and the homogeneity of these findings is reported by Weigel & Weigel (1989).

In addition to the general association of NVP with a decreased risk of miscarriage, there is also an association with a decreased risk of subsequent miscarriage in threatened miscarriage. These results also agree with previous reports (Speert & Guttmacher 1954; Medalie 1957).

Our categorization of NVP into three levels (no symptoms, nausea only, nausea with vomiting) contrasts with the standard dichotomies (no symptoms *vs* nausea, vomiting *vs* no vomiting) used previously. This three-way classification has indicated that it is only vomiting which is associated with decreased miscarriage risk, and that women who have nausea without vomiting have a miscarriage risk equal to that in the population.

In contrast to previous studies, we found no association between NVP and other pregnancy outcomes. NVP has been reportedly associated with slightly longer duration of gestation (Klebanoff *et al.* 1985), a decreased risk of preterm delivery (Klebanoff *et al.* 1985; Tierson *et al.* 1986), a decreased (Brandes 1967; Tylden 1968; Tierson *et al.* 1986) or increased (Kricker *et al.* 1986) risk of low infant birthweight. However, in agreement with our results, Jarnfelt-Samsioe *et al.* (1985) and Klebanoff *et al.* (1985) failed to detect an association between NVP and either birthweight or preterm birth. All these studies excluded miscarriages from their analyses, so it is not clear what factors are responsible for differences in association. Given that the current study showed an association between the confounding variables of maternal age and housewife status with birthweight, the failure of other authors to control for confounders cannot be discounted. The relation between NVP and length of gestation and birthweight needs to be examined further in large multivariable analyses including all relevant confounding variables.

It has been claimed that vomiting (especially hyperemesis) may be associated with increased risk for fetal defects of the skeleton, palate and other soft tissue, independent of anti-emetic use (Najouks 1953; Thalhammer 1953; Hohlbein 1961; Noack 1963; Doring & Hossfeld 1976; Kricker *et al.* 1986). This claim was not substantiated in the current study nor in other recent studies (Klebanoff & Mills 1986; Milkovich & van den Berg 1976). Yerushalmy & Milkovich (1965) found that women with NVP were more likely to give birth to a malformed infant; but since their sample is a subset of the data analysed by Milkovich & van den Berg (1976), in the absence of any indication of bias, the lack of association identified by the latter authors must be accepted.

The large size of our sample increases the confidence that NVP is not associated with length of gestation, birthweight, placental weight, body length, and head circumference.

These variables are measured fairly reliably, so that error of measurement would not be expected to obfuscate group differences. The concurrence of our results with those of previous studies (Wolkind 1982; Kruse *et al.* 1975; Klebanoff *et al.* 1985; Jarnfelt-Samsioe *et al.* 1983) gives increased confidence. Less confidence is placed in the result that NVP is not associated with the more subjective Apgar score, although the virtual identity of the mean Apgar scores across NVP levels appears to make assertion of any association untenable. In contrast, the low rate of perinatal mortality and fetal anomalies (both about 1·0%) precludes confident assertions about lack of association between NVP and these pregnancy outcomes in our study.

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Nausea and vomiting of early pregnancy and pregnancy outcome. A meta-analytical review

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Summary. The generalizability of the apparent decreased risk of miscarriage and perinatal mortality associated with early pregnancy nausea and vomiting was investigated by examining data available from 11 previous studies. Statistical reanalyses of these studies indicated a strong significant association of nausea and vomiting of pregnancy with decreased risk of miscarriage, and no consistent associations with perinatal mortality. A statistical meta-analysis confirmed the decreased risk of miscarriage associated with gestational nausea and vomiting (common odds ratio = 0·36, 95% CI 0·32 to 0·42) and indicated that the association with decreased fetal mortality was restricted to the first 20 weeks gestation. The meta-analysis also revealed that over 150 additional possibly unreported studies with contradictory evidence would be required to refute this observed association.

In a previous study (Weigel & Weigel 1989) of the association of early pregnancy nausea and vomiting (NVP) with pregnancy outcome, the only significant association identified was a decreased risk of miscarriage. The association of NVP with decreased risk of miscarriage (Speert & Guttmacher 1954; Medalie 1957; Yerushalmy & Milkovich 1965; Brandes 1967; Kullander & Kallen 1976; Jarnfelt-Samsioe *et al.* 1983, Petitti 1986), fetal mortality (Klebanoff *et al.* 1985; Tierson *et al.* 1986), and perinatal mortality (Brandes 1967; Tylden 1968; Milkovich & van den Berg 1976) has been reported previously but conclusions about the association of NVP with fetal and neonatal mortality must be tentative. Several studies (Speert & Guttmacher 1954; Yerushalmy & Milkovich 1965; Brandes 1967; Kullander & Kallen 1976; Jarnfelt-Samsioe *et al.* 1983) did not report statistical analyses of the association of NVP with fetal and neonatal mortality. Although other studies presented statistical evidence suggesting an association of NVP with decreased risks of miscarriage (Medalie 1957; Petitti 1986), fetal mortality (Klebanoff *et al.* 1985; Tierson *et al.* 1986) and perinatal mortality (Tylden 1968), the number of confirmatory studies may not be sufficient to demonstrate generalizability. The studies also employ different time intervals for analysis of mortality risk: miscarriage (first 20 weeks gestation), stillbirth (last 20 weeks gestation), fetal death (prenatal mortality), perinatal mortality (stillbirth and neonatal death) and neonatal mortality, so that it is not clear whether the decreased risk of

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mortality is constant during the whole prenatal and neonatal period

The purpose of the current study was to assess the generalizability of the association of NVP with fetal and neonatal mortality, with particular attention to the time of death. The analytical goals are twofold. First, data from previous studies were reanalysed in a formal statistical analysis to obtain quantitative estimates of the association of NVP with fetal and neonatal mortality and to assess their statistical significance. Second, statistical methods of meta-analysis (Glass *et al.* 1981; Rosenthal 1984; Wolf 1986) are applied to assess previous studies with respect to the homogeneity and overall degree of association of NVP with miscarriage and perinatal mortality.

Selection of studies

Potential studies for analysis were identified by searching the MEDLINE data base for the time period of January 1966 (the earliest MEDLINE reference date) to December 1988. References were identified from the intersection of the medical subject headings: 'Pregnancy' and ['Nausea' or 'Vomiting'] Articles covering this area before January 1966 were identified from references cited in the articles obtained from the MEDLINE search.

Studies utilized for data analysis were limited to articles published in English. A study was included only if it was possible to obtain quantitative data (either from direct reporting of frequencies, or where frequencies could be unambiguously established from percentage data) allowing the cross-classification of subjects into a 2×2 contingency table with variable 1 identifying the presence or absence of NVP (either nausea (with or without vomiting) *versus* no nausea, or vomiting *versus* no vomiting (with or without nausea)) and variable 2 identifying the presence or absence of one of the classes of fetal and neonatal mortality (miscarriage, stillbirth, fetal mortality (= miscarriage or stillbirth), neonatal mortality, or perinatal mortality (= stillbirth or neonatal death)). Studies dealing only with hyperemesis gravidarum were excluded.

Ten previous studies met the inclusion criteria for formal statistical analysis of the association of NVP with miscarriage and perinatal mortality (Speert & Guttmacher 1954; Medalie 1957; Yerushalmy & Milkovich 1965; Brandes 1967; Tylden 1968; Milkovich & van den Berg 1976; Kullander & Kallen 1976; Jarnfelt-Samsioe *et al.* 1983; Klebanoff *et al.* 1985; Tierson *et al.* 1986). Details of these 10 studies are listed in Table 1 together with our previous study (Weigel & Weigel 1989). One study that analysed statistically the association of NVP with miscarriage (Petitti 1986) could not be included because it was not possible to determine the frequency counts for all cells in the 2×2 contingency table. One study (Walford 1963) cited by several authors (Yerushalmy & Milkovich 1965; Brandes 1967; Petitti 1986) as indicating a decreased risk of miscarriage with NVP was also excluded because the comparison was not between presence and absence of NVP, but rather between presence and absence of anti-emetic therapy which combined women with

Table 1. Characteristics of the studies included in the overview

Study reference	Location	Time period	Comments
Speert & Guttmacher (1954)	New York City	Early 1950s	Private practice
Medalie (1957)	Rural Israel	1950–52	General practice
Yerushalmy & Milkovich (1965)	Oakland, California	1960–63	Health maintenance organization
Brandes (1967)	Oakland, California	1960–63	Health maintenance organization
Tylden (1968)	London	1951–61	University hospital, psychiatric patients and matched hospital controls
Milkovich & van den Berg (1976)	Oakland, California	1959–66	Health maintenance organization
Kullander & Kallen (1976)	Malmo, Sweden	1963–65	University hospital
Jarnfelt-Samsioe *et al.* (1983)	Goteborg, Sweden	Early 1980s	University hospital
Klebanoff *et al* (1985)	Multicentre, USA	1959–66	Collaborative perinatal project
Tierson *et al.* (1986)	Albany, New York	1976–77	Private practices and obstetrics clinics
Weigel & Weigel (1989)	Los Angeles	1983–84	University hospital

NVP who received no medication with women without NVP.

Reanalysis of previous studies

Analytic methods

For each study meeting the inclusion criteria, a 2×2 contingency table was constructed from available data and the following statistics were calculated. The odds ratio was utilized as a method of association (Fleiss 1981), due to its comparability across different sampling methods (Feinstein 1985), and the development of methods for combining measures of association from different studies (Fleiss 1981). The odds ratio and its 95% confidence interval (CI) were calculated using the Woolf (1955) method, which is recommended to decrease bias in the estimation of the common odds ratio when data are combined from several studies (Gart 1971; Fleiss 1981) The association of NVP with mortality was determined for each prenatal and neonatal time interval for which data were available from previous studies.

Results and discussion

The statistical reanalysis of the 10 previous studies meeting the inclusion criteria, plus the results of Weigel & Weigel (1989), are presented in Table 2. It is apparent that for all seven studies with data on miscarriage, NVP was associated with a highly significant decrease in miscarriage risk. (Six of the seven studies were significant at $P<0{\cdot}001$.) The two studies combining miscarriage and stillbirth as a single outcome also indicated a decreased risk of fetal mortality with NVP, although the relation was not as strong as for miscarriage alone. The two studies with stillbirth as a distinct category did not show a significant association of this outcome with NVP. There was some evidence for an association of NVP with neonatal mortality, with the data of Yerushalmy & Milkovich (1965) revealing a significant association at the $P<0{\cdot}05$ level, whereas the data of Brandes (1967) did not show any association of NVP with neonatal mortality. Of the three studies with a single perinatal mortality category, two (Tylden 1968; Milkovich & van den Berg 1976) indicated a significantly decreased risk of perinatal mortality for NVP.

As expected, the reanalysis confirmed the association of NVP with decreased risk of miscarriage (Medalie 1957), fetal mortality (Klebanoff *et al.* 1985; Tierson *et al.* 1986), and perinatal mortality (Tylden 1968) for the previous studies employing inferential statistical methods. For the previous studies reporting an association of NVP with decreased risk of offspring mortality without formal statistical analysis, statistical significance of the association was verified for decreased risk of miscarriage (Speert & Guttmacher 1954; Yerushalmy & Milkovich 1965; Brandes 1967; Kullander & Kallen 1976; Jarnfelt-Samsioe *et al.* 1983) and perinatal mortality (Milkovich & van den Berg 1976). An association reported previously without the support of inferential statistics that was not confirmed with formal reanalysis was the assertion by Brandes (1967, p.429) that NVP is associated with decreased perinatal (particularly neonatal) mortality On the other hand, although Yerushalmy & Milkovich (1965) did not report a decreased risk of neonatal mortality with NVP, the statistical reanalysis identified this association. However, since the Yerushalmy & Milkovich (1965) data sample is a subset of the larger sample presented in Brandes (1967), the absence of a relation between NVP and perinatal mortality identified in the reanalysis of the Brandes (1967) data is a more precise estimate of the true association.

Meta-analysis

Analytical methods

The studies in Table 1 were considered for the meta-analysis. The only criterion for exclusion was non-independence of study samples. There were three studies (Yerushalmy & Milkovich 1965; Brandes 1967; Milkovich & van den Berg 1976) of patients from the prenatal care clinics of the Kaiser-Permanente Hospitals, a health maintenance organization (HMO) in the Oakland, California area. Of these, Brandes (1967) was selected for the meta-analysis because it was the largest of the samples that distinguished mortality by three intervals (<20 weeks gestation, >20 weeks to birth, neonatal period).

Although the formal statistical analysis provides the strongest evidence for decreased risk of miscarriage with NVP, some evidence exists for decreased mortality risk for each of the three time intervals (first 20 weeks gestation, last 20 weeks, neonatal mortality). The purpose of the meta-analysis is to estimate the duration of the

Table 2. Reanalysis of previously published data: association of nausea and vomiting of pregnancy (NVP) with miscarriage and perinatal mortality*

Study	*n*	NVP rate (%)	Specified outcome: NVP	Yes	No	% yes	Total (%)	χ^2	Odds ratio	(95% CI)	*P*
Fetal deaths <20 weeks gestation (miscarriage)											
Speert & Guttmacher (1954)	256	64·5	Pres	8	157	4·8	12·1	21·11	0·16	(0·07 to 0·36)	<0·001
			Abs	23	68	25·3					
Medalie (1957)[(a)]	100	52·0	Pres	0	52	0·0	11·0	11·15	0·03	(0·00 to 0·54)	<0·001
			Abs.	11	37	22·9					
Yerushalmy & Milkovich (1965)	3853	71·1	Pres	104	2636	3·8	5·7	63·33	0·34	(0·26 to 0·45)	<0·001
			Abs	116	997	10·4					
Brandes (1967)	7027	72·8	Pres	145	4972	2·8	3·9	52·11	0·41	(0·32 to 0·53)	<0·001
			Abs.	126	1784	6·6					
Kullander & Kallen (1976)	5377	71·7	Pres	212	3645	5·5	7·9	104·61	0·36	(0·30 to 0·44)	<0·001
			Abs	211	1309	13·9					
Jarnfelt-Samsioe *et al* (1983)	911	69·7	Pres	28	607	4·4	6·1	10·00	0·41	(0·24 to 0·70)	<0·01
			Abs	28	248	10·1					
Weigel & Weigel (1989)	903	69·3	Pres	12	614	1·9	3·5	14·29	0·25	(0·12 to 0·52)	<0·001
			Abs	20	257	7·2					
All fetal deaths (miscarriages + stillbirths)											
Klebanoff *et al* (1985)[(b)]	7972	56·4	Pres.	153	4347	3·4	4·2	17·00	0·63	(0·51 to 0·78)	<0·001
			Abs	184	3288	5·3					
Tierson *et al* (1986)	424	89·6	Pres	35	345	9·2	10·4	4·22	0·38	(0·17 to 0·85)	<0·05
			Abs	9	35	20·5					
Fetal deaths ≥20 weeks gestation (stillbirths)											
Yerushalmy & Milkovich (1965)	3853	71·1	Pres	59	2681	2·2	2·2	0·00	0·95	(0·59 to 1·51)	NS
			Abs	25	1088	2·2					
Brandes (1967)	7027	72·8	Pres	105	5012	2·1	2·1	0·00	0·97	(0·67 to 1·40)	NS
			Abs	40	1870	2·1					
Perinatal mortality (stillbirths + neonatal mortality)											
Tylden (1968)[(b)]	466	33·0	Pres	1	153	0·6	3·6	4·68	0·18	(0·03 to 0·94)	<0·05
			Abs	16	296	5·1					
Milkovich & van den Berg (1976)	10 441	61·6	Pres	198	6234	3·1	3·5	9·08	0·72	(0·59 to 0·89)	<0·005
			Abs	169	3840	4·1					
Weigel & Weigel (1989)	903	69·3	Pres	6	620	1·0	1·0	0·03	0·82	(0·22 to 3·03)	NS
			Abs	3	274	1·1					
Neonatal mortality											
Yerushalmy & Milkovich (1965)	3858	71·1	Pres	28	2717	1·0	1·3	4·94	0·51	(0·29 to 0·89)	<0·05
			Abs	22	1091	2·0					
Brandes (1967)	7027	72·8	Pres.	61	5056	1·2	1·3	1·28	0·75	(0·48 to 1·16)	NS
			Abs	30	1880	1·6					

* All NVP distinctions are no NVP *vs* nausea (with or without vomiting), unless indicated thus (a) distinction is none/mild *vs* moderate/severe, (b) distinction is vomiting *vs* no vomiting (with or without nausea)

Pres., Present, Abs., absent, NS, not significant.

prenatal and neonatal interval where NVP is a prognostic indicator of decreased mortality risk. Ideally, the overall association between NVP and mortality would be examined separately for each of the three time intervals. But except for the first 20 weeks gestation, there were not more than two studies which met the inclusion criteria for the meta-analysis in any given time interval. Therefore, the following approach was used to determine whether the decreased mortality associated with NVP covered in effect the entire prenatal and neonatal period, or whether statistical evidence existed to designate a more limited time interval. First, studies covering any time interval during the prenatal and neonatal period were analysed. The second analysis narrowed the time interval to exclude the neonatal period, the third was confined to data relating to miscarriage.

The statistical methods employed for combining data from different studies are those outlined in Fleiss (1981). The overall association between NVP and mortality during the time interval examined, apparent from the common odds ratio (and its 95% CI), was calculated by weighting the results from the individual studies (sample size is the primary determinant of this weighting). Then the homogeneity of the estimates of the odds ratios among samples was assessed, with a *P* value greater than 0·05 (rather than less than) for the homogeneity χ^2 chosen as the criterion for acceptable homogeneity. Evidence supporting the hypothesis that NVP is associated with decreased mortality during the entire interval is provided statistically by a combination of a significant common odds ratio and a demonstration of the homogeneity of this association.

One criticism of the meta-analytical statistical evaluation of published reports is that studies with non-significant results fail to be published; thus, published studies may be a biased sample of data analyses conducted for the hypothesis under examination (Rosenthal 1979; Kraemer & Andrews 1982). Statistical methods have been developed to estimate the number of additional studies with evidence contradictory to the observed overall association that would be required to nullify the observed significant relationship. This *fail-safe n* was calculated using the methods described in Wolf (1986).

Results and discussion

Table 3 lists a common odds ratio of 0·47, indicating a decreased risk of mortality with NVP, when data are combined from the entire prenatal and neonatal period; this association is highly significant (association χ^2 (1 d.f.) = 179·20, $P<0·001$) although the results

Table 3. Results of meta-analysis for entire prenatal–neonatal time interval

					Time interval included (weeks)		
Study	*n*	Odds ratio	*Weight*	χ^2	< 20	> 20	Neonatal
Speert & Guttmacher (1954)	256	0·16	5·5	18·88	X		
Medalie (1957)	100	0·03	0·5	5·65	X		
Kullander & Kallen (1976)	5377	0·36	95·5	99·18	X		
Jarnfelt-Samsioe *et al* (1983)	911	0·41	13·2	10·54	X		
Klebanoff *et al.* (1985)	7972	0·63	80·2	17·20	X	X	
Tierson *et al.* (1986)	424	0·38	6·1	5·57	X	X	
Brandes (1967)	7017	0·56	110·0	36·48	X	X	X
Weigel & Weigel (1989)	903	0·33	9·8	12·13	X	X	X
Tylden (1968)	466	0·18	1·2	3·52		X	X

Common odds ratio 0·47, 95% CI 0·43 to 0·53

Partitioning of χ^2

	χ^2	d.f	*P*
Total χ^2	209·15	9	<0·001
Association χ^2	179·20	1	<0·001
Homogeneity χ^2	29·96	8	<0·001

Table 4. Results of meta-analysis for entire prenatal time interval

Study	*n*	Odds ratio	*Weight*	χ^2	Time interval included (weeks)	
					< 20	> 20
Speert & Guttmacher (1954)	256	0·16	5·5	18·88	X	
Medalie (1957)	100	0·03	0·5	5·65	X	
Kullander & Kallen (1976)	5377	0·36	95·5	99·18	X	
Jarnfelt-Samsioe *et al* (1983)	911	0·41	13·2	10·54	X	
Weigel & Weigel (1989)	903	0·25	7·4	13·91	X	
Klebanoff *et al* (1985)	7972	0·63	80·2	17·20	X	X
Tierson *et al.* (1986)	424	0·38	6·1	5·57	X	X
Brandes (1967)	7017	0·55	92·9	32·28	X	X

Common odds ratio 0·47, 95% CI 0·42 to 0·52

Partitioning of χ^2

	χ^2	d f	*P*
Total χ^2	203·22	8	<0·001
Association χ^2	173·81	1	<0·001
Homogeneity χ^2	29·40	7	<0·001

are very heterogeneous (homogeneity χ^2 (8 d.f.) = 29·96, $P<0·001$). Table 4 indicates that excluding the neonatal period (only Tylden (1968) is excluded) does not change the overall degree of association or decrease heterogeneity. However, Table 5 reveals that when only the first 20 weeks gestation are included, the common odds ratio is decreased to 0·36 (association χ^2 (1 d.f.) = 189·67, $P<0·001$), and the criterion for homogeneity is met (homogeneity χ^2 (5 d.f.) = 8·87, $P>0·10$)

Table 5 also indicates that to invalidate the

Table 5. Results of meta-analysis for first 20 weeks gestation

Study	*n*	Odds ratio	*Weight*	χ^2
Medalie (1957)	100	0·03	0·5	5·65
Speert & Guttmacher (1954)	256	0·16	5·5	18·88
Weigel & Weigel (1989)	903	0·25	7·4	13·91
Kullander & Kallen (1976)	5377	0·36	95·5	99·18
Jarnfelt-Samsioe *et al.* (1983)	911	0·41	13·2	10·54
Brandes (1967)	7017	0·41	64·4	50·39

Common odds ratio 0·36, 95% CI 0·32 to 0·42

Partitioning of χ^2

	χ^2	d f.	*P*
Total χ^2	198·55	6	<0·001
Association χ^2	189.67	1	<0·001
Homogeneity χ^2	8.87	5	>0·1

	Alpha level	
	0·05	0·01
Fail-safe *n*	343	168

observed decreased risk of miscarriage associated with NVP, the number of additional studies with contradictory evidence required (fail-safe n) is 168 if the 0·01 level of statistical significance is chosen as an alpha level, and 343 studies if the 0·05 alpha level is chosen. Rosenthal (1979) suggests a criterion of fail-safe $n>5k+10$, where k = number of studies in the meta-analysis, as indicating generalizability of published results. In the current analysis of six previous studies of the association of NVP with miscarriage, the minimum fail-safe n criterion is $5k+10=40$, which is considerably less than the requirement of 168 non-significant studies to contradict the observed results at the stricter 0·01 alpha level. Thus, it is extremely unlikely that additional studies will contradict the conclusion drawn here that NVP is associated with a significant decrease in miscarriage.

The association of NVP with decreased risk of fetal mortality in early pregnancy has been reported from various geographical areas including: USA (Speert & Guttmacher 1954; Brandes 1967; Klebanoff *et al.* 1985; Tierson *et al.* 1986; Weigel & Weigel 1989); Sweden (Kullander & Kallen 1976; Jarnfelt-Samsioe *et al.* 1983); England (Tylden 1968); Israel (Medalie 1957), and also for ethnically diverse populations within the United States including: 97% white (Tierson *et al.* (1986); 57% Hispanic and 27% white (Weigel & Weigel 1989); 67% white and 33% black (Klebanoff *et al.* 1985). Thus, the phenomenon of reduced risk of miscarriage for women with NVP is apparently not restricted by cultural, genetic, or environmental variability.

The evidence from the reanalysis and meta-analysis indicates that the decreased mortality risk associated with NVP is restricted to the first 20 weeks gestation, and was not detected during the last 20 weeks or in the neonatal period. Although the meta-analysis of the overall association of NVP with mortality throughout the prenatal and neonatal period identifies a significant common association, there is also heterogeneity.

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A randomized study of a domiciliary antenatal care scheme: the effect on hospital admissions

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Summary. A preliminary randomized study has been made of a domiciliary management scheme which incorporates telephonic fetal heart rate monitoring for women with high-risk pregnancies. In this paper we report effects of the scheme on the pattern of hospital admissions. Sixty women were randomized 2:1 for domiciliary surveillance or for conventional hospital care, with 40 and 17 records finally available for analysis. The groups were well matched for maternal, obstetric and socio-economic characteristics. In the domiciliary group, 21 (53%) of the women avoided hospital admission altogether, the admission rate was more than halved, and the mean proportion of the time spent in hospital was reduced from 50% to 16% of the observation period. The women who received domiciliary care were generally satisfied with the scheme. Our study confirms expectations that carefully planned domiciliary surveillance can reduce the number and duration of hospital admissions.

Domiciliary surveillance using recently introduced telephone fetal monitoring systems (Currie & Dalton 1986; Gough *et al.* 1986) is expected to reduce the number and duration of hospital admissions for some women with high-risk pregnancies. The *prima facie* case is largely based on the belief that admissions are lengthy, are mainly for fetal monitoring, and that women will usually prefer to remain at home even with potentially complicated pregnancies

We have introduced a comprehensive package for domiciliary surveillance called the Cardiff Integrated Antenatal Care (CIAC) scheme The CIAC scheme is based on midwifery expertise and on facilities provided in the woman's home similar to those normally provided in hospital (Middlemiss *et al* 1987). The scheme incorporates the use of our telephonic domiciliary fetal monitoring system (DFM) (Dawson *et al.* 1988). We have carried out a preliminary randomized controlled study, primarily to determine the effect of our management policy on maternal psychological measure (Middlemiss *et al.* 1989). We were also interested in other considerations, and in this paper we report the effect on the number and duration of antenatal hospital admissions, and patients' attitudes to the new management. Detailed midwifery and other implications of the CIAC scheme will be discussed elsewhere.

Patients and methods

All eight obstetric consultants in South Glamorgan agreed to refer women to the study over

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an 18-month period. The consultants were asked to check the patient's suitability for the study in that each woman had to have a stated primary risk factor which would normally have led to admission, and the woman needed to be sufficiently literate to understand a written questionnaire. Women were excluded if the consultant considered immediate intervention was likely, and this was rechecked by ourselves before randomization (there was one exclusion for this reason). Women were not excluded through having multiple pregnancies, or for not having a telephone, as suitable arrangements can usually be made with neighbours or by using a Cellnet telephone.

After selection, the trial was explained and consent was sought. We used 2:1 randomization in allocating women either to care under the CIAC scheme (domiciliary group) or to conventional hospital care. This gave maximum trial to the new method with minimal loss of statistical power (Pocock 1983), anticipating that the conventional group would be representative of general experience in this area. The size of the trial was chiefly determined by the primary psychological outcome, described in detail elsewhere (Middlemiss *et al.* 1989). We had calculated that 60 patients were required overall to give an 80% chance at the 0·05 significance level of detecting a change of at least five points in the psychological measures.

Sixty-five women were initially approached consecutively via the antenatal clinics, and at this stage five women declined randomization, expressing preference for hospital care. After admission to the trial a sealed envelope was opened by a third party to reveal the management allocation.

Table 1. Descriptions of the characteristics of the domiciliary and conventional groups at entry to the study

	Domiciliary (n=40)	Conventional (n=17)
Maternal age (years)		
Mean (SD)	28·78 (5·85)	26 06 (3·51)
Range	17–41	19–33
Parity		
Range	0–4	0–7
Percent nulliparous	47·5	41·2
Gestation at entry (weeks)		
Mean (SD)	35·25 (3·79)	35·06 (3·29)
Range	26–41	29–41

There were no significant differences between the groups; Mann–Whitney test

Plans for care, including antenatal clinic visits, were jointly formulated for each woman allocated to the domiciliary group. Comprehensive care and support were then provided regularly in the home by one of two midwifery research sisters both with background experience as senior hospital midwives (Middlemiss *et al.* 1987). The duration and frequency of the home visits was determined by the individual needs of the women. There was frequent communication between the pregnant woman, midwife and the referring consultant team, who continued to make any clinical decisions. During periods when there were fewer eligible referrals, we deliberately complemented the clinical workload of the staff by accepting referrals outside the study.

The women allocated to conventional care were admitted to hospital under the normal arrangements for each consultant. Similarly, any subsequent discharge and antenatal clinic visits took place in the normal way.

The proportion of time before the onset of labour spent in hospital was calculated for each woman. The number of days spent in hospital was expressed as a percentage of the days from admission to the study to the onset of labour or elective caesarean delivery. For collective analysis these percentages were then used as a continuous variable. A simple non-attributable questionnaire was completed by all the women at the end of the pregnancy, intended to reveal any overt general satisfaction or dissatisfaction with the scheme.

Results

One record was lost from the domiciliary group and two records from the conventional group, because of failure to record sections of the data, leaving 40 and 17 records available for analysis. However, retrospective inspection of the hospital records did not suggest that omission of data from the three patients would create any bias. No multiple pregnancies were referred, and 28 (70%) of the domiciliary group and 11 (65%) of the conventional group were telephone subscribers.

The randomization produced matching of the groups for maternal age, parity, and gestational age on entry to the study as shown in Table 1. Additionally, the groups were well matched for

Table 2. Admissions and other measures of outcome in the domiciliary and conventional groups

	Domiciliary (n=40)	Conventional (n=17)	Risk ratio (95% confidence interval)
Admissions			
No. of women admitted (%)	19 (48)	17 (100)	0·48 (0·34–0·65)
No. of admissions	23	26	
Admissions per patient			
Mean (SD)	0·58 (0·68)	1·53 (0·80)**	
Range	0–2	1–4	
Gestation at delivery (weeks)			
Mean (SD)	38·78 (2·12)	38·65 (2·09)NS	
Range	32–42	35–42	
Days under observation			
Mean (SD)	25·40	27·06*	
Range	2–78	1–80	
Proportion of observation period spent as in-patient (%)			
Mean (SD)	16 (27)	50 (34)***	
Range	0–96	7–100	
Obstetric interventions			
Induction rate (%)	28	18	1·56 (0·55–5·89)
Overall section rate (%)	30	35	0·85 (0·39–1·98)
Emergency section rate (%)	25	24	1·06 (0·41–3·24)

NS, Not significant (Mann–Whitney)
** $P<0·01$ (Mann–Whitney)
*** $t=4·02$; $P<0·001$.

marital status, socio-economic category, and indications for referral, which were: suspected small-for-dates fetus, hypertension, antepartum haemorrhage, poor obstetric history, reduced fetal movements, and unexplained weight loss with proteinuria.

The two groups spent similar mean periods under observation and had a similar duration of pregnancy (Table 2) Obstetric intervention rates were not markedly different, and there were no perinatal losses in either group.

In the domiciliary group, 21 women (53%) spent no nights at all in hospital, confirming a considerable reduction in the number of women requiring admission, and the admission rate was more than halved. Ten women (25%) of the domiciliary group spent more than 5 nights in hospital, compared with 11 (65%) of the conventional group.

Not only was the number of admissions reduced but there was a striking reduction of 34% in the proportion of time spent in hospital (Table 2), with a 95% confidence interval (CI) for the mean difference of 15%–53%. This effect was seen even if women in the domiciliary group who were admitted are considered separately (22% of the observation period in hospital).

When admission did take place on 23 occasions in 19 of the women in the domiciliary group, nine admissions were for hypertension, three for antepartum haemorrhage, seven for fetal heart rate abnormalities (six were later confirmed to have decelerations), and four for other reasons.

The 40 women in the domiciliary group received 450 home visits of which only six were required out of hours. This represented 435 h of visiting in the home and a closely estimated 75 miles of travelling per patient (maximum 126 miles). The pure service commitment for the midwives, aside from research duties, amounted to less than one half of a whole time equivalent each in an area with 6000 deliveries annually None of the women in the domiciliary group expressed any major dissatisfaction with the service, although one minor comment was received about the timing of visits

Discussion

Our study confirms the expectation that a clinical policy which incorporates a distant fetal monitoring system can markedly reduce both the number and the duration of hospital admissions. The reduction in admissions can be accomplished without depriving women of at least a similar level of care to that provided in hospital. Nevertheless, a small number of women who were eligible for the study preferred not to risk being allocated to remaining at home. Other aspects of the value of fetal monitoring fall outside the scope of this paper.

To date this form of care appears to be neither more nor less favourable in terms of obstetric outcome, but larger studies will be required to allow satisfactory comparison. It is important to note that women from the domiciliary group who did require admission were potentially at increased risk when compared with the reference group, and yet they spent a considerably smaller proportion of their time in hospital. None of the admissions in either group was solely for fetal monitoring. This reaffirms our view that fetal monitoring should only be carried out within a full clinical context. Few of the antepartum admissions in the conventional group were considered to be for the duration of the pregnancy.

The economic benefits to both the women and the health service have yet to be established but it is notable that this study alone represents a potential overall saving of 345 nights in hospital for 40 women. For those women who did not have a telephone there was no great difficulty in making workable arrangements. Our conclusions from this study are necessarily limited, but we are encouraged to carry out more extensive and discriminating audits in different settings. The management system holds promise for promoting better justified intervention: the greatest potential may be with women who would *not* ordinarily be admitted to hospital but who might benefit from additional domiciliary support and surveillance.

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The development and implementation of a computerized on-line obstetric record

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Summary. We developed and implemented a completely paperless and on-line obstetric record in the high-risk obstetric clinics at Columbia Presbyterian Medical Center. Patient care and interactions are input directly into the computer by the health care providers. Laboratory information is transferred automatically from the Laboratory Information Service into the computerized prenatal record. The system has been in continuous operation for 2 years and is highly regarded. Problems such as illegible handwriting, missing records, and missing laboratory data have disappeared. Research and data query capabilities have been facilitated. The feasibility and applicability of a computerized record replacing the paper record has been demonstrated.

Because obstetrics is a well-defined field and focuses on events that occur within a defined interval of 9 months, it lends itself well to computerization. A number of different systems have been developed (Houlton *et al.* 1984, Jennett & Warford 1982; Lilford & Chard 1981; Maresh *et al.* 1983, 1986; Sokol & Chik 1982; Stead *et al.* 1977). Some of these systems (Jennett & Warford 1982) use multiple paper forms for initial assessment and for the antepartum, intrapartum, and newborn records. Each form has discrete boxes and areas for entering data in defined ways and in general follows a problem-oriented record approach (McDonald 1976; Weed 1969). Multiple copies of each sheet are made and one copy is sent to a batch entry clerk who enters the data into the computer. Once the data are entered, summary reports and statistics can be generated. Also if the data are entered promptly, there are equations and algorithms that will define risks such as the possibility of preterm labour. Some on-line systems have been developed on microcomputers in the labour and delivery suite (Houlton *et al.* 1984; Maresh *et al.* 1983, 1986) while others are for office management (Leppert *et al* 1985) Other systems are more interactive (Lilford & Chard 1981) and the feasibility of replacing the paper record with a computerized record has been clearly shown (Lilford *et al.* 1982) as has its acceptance by the health care providers (Brownbridge *et al.* 1988)

There are problems with these systems. The basic record is still a paper record which can be lost. Also, data entry is subject to errors Even with a computer in every clinic, the process is still one of batch entry The fruits of computerization are provided by risk assessment reports and by summary statistics for administrative, educational, and research purposes. However, these benefits are available to only a few health care professionals and only after the delay of data entry In addition to the problem of lost pieces of paper, the system is subject to errors caused by illegible handwriting. Moreover, there is no on-line retrieval of laboratory data and no graphics are available at the bedside; indeed, the power of the computer is not brought to the bedside. Trends cannot be analysed and only the select few who have access to

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the main-frame can resolve statistical questions or assess data for research purposes. Even the systems developed for use on labour and delivery are for very specific purposes (Houlton *et al.* 1984; Maresh *et al.* 1983, 1986) and are limited in their ability to retrieve laboratory data from other computers, networking, and still involve keying in data from a paper record.

At the Columbia-Presbyterian Medical Center, we decided to develop a 'real-time, live' computer system that would completely replace the paper record. The physician would actually be seeing the patient, using only the computerized prenatal record.

Material and methods

The system

In collaboration with AT&T Bell Laboratories, we developed a complete computerized system for recording prenatal records and installed it in the high-risk clinics in the Perinatal Center. The heart of the system is a 3B2/600 computer with another 3B2/400 acting as an automatic back-up. AT&T personal computers, PC6300s, which serve as terminals, have been placed in all patient areas, including the front desk, examination rooms, consultation rooms, and physicians' offices. The system runs the UNIX operating system, with the UNITS database management program, and extra programming in C language.

Each patient's entire prenatal record is placed on-line, including demographics, medical, family, gynaecological and obstetric history, general physical and pelvic examinations, prenatal visits, laboratory data, and appointments. The software consists of a User Executive program at the terminal that interphases with the central 3B2 processor. At the 3B2 level there are a number of application servers that are either in memory or loaded from the disk, depending on the memory limits of the system. These applications then interact with the patient database. Parallel to this are the security profiles, form definitions, and menu definitions, which interact with the User Executive program to produce the terminal display. These are at the Visual Editor and data dictionary management system level. This program then interacts with the data dictionary. System administration occurs at this level. The database definitions then interact directly with the patient database.

Word processing capabilities are available for free text entry. Pick fields are extensively used in the system and there are customized menus, function keys, and a command line for those more familiar with the system, as well as specified hard keys with specialized functions. Summaries are available for quick reviews, as are 'canned' reports and graphics.

Laboratory data are transferred automatically from the Laboratory Information System which is a completely separate computer system. The laboratory uses an HP 1000 to store and transmit data throughout the hospital, using its own terminals. This system automatically interphases with the Outpatient Clinical Information System (OCIS) through the Gateway System. Basically, this is a 3B2/400 computer which analyses all of the data transmitted out of the HP1000. The system checks for errors by comparing the patient's name and unit number. Once checked and the system recognizes the data as belonging to the OCIS system, the data are automatically transferred and placed in the appropriate record on the local computer or 3B2/600. The health care provider accesses the record, sees the laboratory results and, in the event of an error, can either discard the data or acknowledge the data as correct in spite of the mismatch. Limits for abnormal values in laboratory data, such as haematocrit value of less than 30, are placed into the system so that the system will recognize them and automatically alert the health care provider through its electronic mail capability

Use of the system

When a patient comes to the clinic, her appointment is checked, the nurse takes the vital signs, weighs the woman, checks the urine, and records the results on the keyboard. The physician then sees the patient and uses the on-line record to review her history and prenatal care. The record is also problem oriented; there are summary screens for the problems as well as for any medications the patient is taking. The physician can quickly scan through a few summary screens such as the Obstetrical History, Problem List, Summary of Prenatal Visits, and Available Laboratory Data, and know how to treat the patient. The physician saves the data and the nurse then picks up any referrals, orders, or other relevant information directly from the computer at the nurse's own terminal Once the visit is over, the summary is printed via the system laser printer. The summary is put into the permanent paper record that is still required by the hospital. An appointment is made at the same time; the appointment slip is printed by the laser printer and given to the patient.

There is a computer terminal in the labour and delivery area so the health care provider has access to the patient's on-line chart. Outcome and delivery data can be input on the labour suite. If the patient is not delivered but, for example, is placed on a regimen of tocolytics, the physician can enter this information and schedule an appointment without having to call the secretary at the clinic.

Results

The high-risk obstetric clinic has been completely computerized. As a consequence, time is saved and continuity of care assured. The computerized on-line prenatal record offers clear advantages in its reliability and readability, as well as its provision of quick access to critical patient information and to statistical and managerial information.

The users of the system include licensed practical nurses, registered nurses, secretaries, clerks, residents, fellows, and attending physicians. We have found that it is helpful for users to receive some training so they can benefit from the full power of the system, but many practitioners do only 'hands on' work and direct occasional questions to their fellow workers. Residents rotate through the clinic every quarter, so that there is a constant influx of new users. In general, users of the system have accepted the system well, and once familiar with it, have offered a torrent of helpful suggestions on how it could be improved.

Because of the automatic transfer of data for the perinatal system through the Gateway system, the problems of lost laboratory data and time wasted in looking for data have been eliminated, as have difficulties caused by illegible handwriting. In addition, graphics and query capabilities are available. For example, haematocrit values or any numerical laboratory data are graphed over time to see if there is a general trend. The information can be summarized in tabular form or displayed graphically.

Alert systems have been implemented so abnormal tests are always identified. If, for example, an abnormal glucose challenge test comes through the system, this information is automatically sent by electronic mail to the health care provider. Once the provider logs on and looks through the mail, the abnormal test is shown so appropriate action is taken.

Other benefits of this computer system include automatic generation of reports of numbers of patient visits, types of problems, and estimated dates of confinement distribution. Statistical analysis and research are performed by an interface with the BMDP statistical package or any package that can access a standard ASCII file. Additional advantages occur because the terminals are actual personal computers, so word processing, database packages, telecommunications, and others are used at a local level.

Networking of the system with computers in other areas such as the antenatal testing centre, the ultrasound area, and other clinic sites permits quick and easy transfer of data. There is no need to make phone calls to obtain laboratory results. Patient's charts are sent to or accessed by staff members in any areas as long as those individuals have security clearance; thus, the loss of charts or information is eliminated.

There is a query language that can identify populations or subpopulations defined by certain criteria. Customized reports are provided. In addition, data can be downloaded to an ASCII file and interphased with standard statistical packages such as SPSS or BMDP. The assessment of clinical data or protocols for research or other purposes is therefore greatly facilitated and enhanced.

It must be noted, however, that a number of disadvantages have appeared with the use of this computer system. The biggest problem is processing speed. The expectation is of almost instantaneous data entry; so, frustrations mount when the user waits for a screen to appear. Specifically, the summary displays of clinical information take too long to be presented on the screen; reports are too slow for interactive use; there is a tremendous variability in response time, depending on the application; and there are too many screens.

As the system evolved and improvements were made, it became clear that the health care personnel bypassed certain characteristics of the system. For example, physicians would type out problems and plans in a free text field in the MD plans section so the nurse could pick up any orders. Since these notes would be summarized in a report if requested, the clinician had all of the information needed to take care of the patient and the problem list was being bypassed. This meant there was no way of asking the system what kinds of patients were being seen. The system was helping to deliver care to the patients but not providing research, or statistical information. In response to these failures to use the system appropriately, training was increased to make personnel aware of the need for accurate reporting of clinical problems, and a reminder note was added to the final screen instructing users to go to the problem list. One possible future change is to modify the system to take users straight to the problem list instead of allowing free text entry at the end of the clinic visit.

Individuals' typing skills or lack thereof also dictated the acceptance or non-acceptance of the system. People who knew how to type had no problems interacting with the computer through the keyboard. However, personnel who did not know how to type complained of the lack of interphases such as light pens, touch screens, and voice recognition packages. A number of solutions have been included to minimize the need for typing. Discrete fields are now used for displaying data such as blood pressure, fetal heart location, and fetal heart rate. A feature called a pick field is used extensively. A pick field is one in which only a discrete number of options can be scrolled through so that the user can select one. For example, in the Presentation field, options such as Vertex, Breech, Transverse are shown; the user can either pick the number of the option or scroll through the different choices and hit return when the appropriate one is available. Other solutions included a menu-driven system and extensive use of windows with extensive options lists.

Hardware enhancements have improved performance. These include using a more powerful processor, the 3B2/600 CPU 2·3 MIPS as opposed to 1·1 on the 3B2/400. The disk of this processor is twice as fast as that of the 1·1 and its memory is also greater, up to 16 MB. Thus, applications can all be loaded into memory instead of being read from disk. The EPORTS card that has been added to control the terminal and printer I/O is faster than the original PORTS card, providing 9600 bps *vs* 1200 bps. Software enhancements have included extra programming to use INDEXED files as much as possible to increase report writer speed. A newer version of UNITS (2·0) was also added as well as an advanced version of UNIX SVR3 that provides pagination. Pregnancy check-up files needed to be revised to reduce database access in the most labour-intensive part of the system, i.e. actual data entry by the health care provider. On-line summaries needed to be maintained as part of the database since, in the present mode, they were generated each time they were requested.

Conclusions

Computerization of our obstetric clinic has been achieved through the development of a complete on-line obstetric record, as well as the design, installation, and implementation of a complete computer system and network. This system differs from others used in obstetric settings in that it is not a batch entry system. All health care providers interact directly with the system; all relevant information is stored on the computer and available to the health care providers on 'real-time'.

The many advantages of this system include clarity and accuracy of data, easy retrieval of patients' charts, and the elimination of the need to call for laboratory data or to wait for laboratory report slips, since these are added automatically through the computer network. The system has been readily accepted and has been in continuous use. Clinical research is done easily and accurately since the data are already on-line.

One disadvantage of the system is lack of portability—one cannot carry the computer along under one's arm. There is also the potential for loss of data, although this has not occurred, as well as the risk of down time because of mechanical or electronic failure, which has occurred. 'Computerphobia' is present among the system's users, depending on their age and typing capabilities. Younger physicians who have grown up with computers adapt more readily than older members of staff who cannot type and who have spent years using the paper chart.

Is the clinic functioning better or worse with the computerized paper record? The computerized record has improved patient care. The problem of lost charts has all but disappeared except for new patients who arrive without a chart. The problem of missing laboratory data has disappeared. The wasted time searching for charts and results has been diminished considerably. Because the system is networked, telephone, verbal, and paper traffic between the department of ultrasound, the antenatal testing centre, and the perinatal clinics has decreased, and, consequently, the time spent on actual patient care by the nurses has increased. Other health care providers who do not spend any time looking for laboratory data have not had their work improved as much. However, the availability of the chart has improved the service provided to the patients. Gone is the process of repeating the entire history to try to determine what is occurring with a particular patient. The physician therefore also has a time saving. Overall, the on-line obstetric record has real value and has been well accepted by all members of the health care team.

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Do raised serum luteinizing hormone levels during stimulation for in-vitro fertilization predict outcome?

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Summary. Previous reports associating raised LH concentrations with reduced fertilization and pregnancy rates in women undergoing in-vitro fertilization (IVF) have assumed a Gaussian distribution of LH values with IVF treatment. We have determined the serum LH range during ovarian stimulation for IVF with a single regimen of clomiphene citrate/hMG from 102 consecutive IVF conception cycles. The results show a non-Gaussian distribution of LH values. Application of this LH range to a consecutive series of 596 women undergoing IVF treated with this single regimen showed no difference in pregnancy rates, fertilization rates, median number of oocytes fertilized or retrieved when analysed with respect to serum LH concentrations above the 75th or 95th centile for $\geqslant 3$ days of an IVF treatment cycle. We conclude that follicular-phase LH concentrations do not predict IVF fertilization rates or clinical outcome and are not clinically useful in individual patient management.

It has been reported that follicular-phase concentrations of serum or urinary luteinizing hormone (LH) can predict fertilization and pregnancy rates in women undergoing ovarian stimulation for in-vitro fertilization (IVF) (Stanger & Yovich 1985; Howles *et al.* 1986). It was suggested that both the fertilization rate of mature oocytes and the subsequent pregnancy rate were reduced in women whose LH concentration was above the arithmetic mean LH concentration during IVF treatment. If confirmed, such observations would be clinically important in predicting likely success during an IVF treatment cycle and perhaps could avoid unnecessary procedures and expense. Moreover, confirmation of these findings in humans would confirm and expand knowledge from animal studies suggesting that atypical gonadotrophin levels can impair fertilization and embryo growth (Moor & Trounson 1977).

In the publications where it is suggested that raised LH concentrations are associated with reduced fertilization and pregnancy rates (Stanger & Yovich 1985; Howles *et al.* 1986) statistics for a Gaussian distribution, computing an arithmetic mean, standard deviation and standard errors, were used. This presupposes that LH values during ovarian stimulation for IVF follow a normal distribution, but this would be surprising, given that 15–20% of women undergoing IVF demonstrate a surge increase in serum LH as they approach the time for oocyte

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retrieval (Jones 1985). Log transformation of serum LH values has been used for other LH analyses, but not, as far as we know, for IVF studies.

In the management of women undergoing IVF, we consider it important to establish what is a desirable serum LH concentration for each day of the treatment. Previous investigations of LH concentrations during ovarian stimulation for IVF included reports analysing cycles arising from more than one type of stimulation regimen (Stanger & Yovich 1985), IVF cycles that were non-conceptual as well as conceptual (Stanger & Yovich 1985), exclusion of patients with an endogenous LH surge (Howles *et al.* 1986) and use of a selected rather than consecutive series of cycles (Howles *et al.* 1986).

For most hormones in gynaecological endocrinology it is important to establish the normal range but, as far as we know, there are no standardized criteria for a normal LH range in IVF programmes. A successful IVF treatment cycle is one that results in a clinical pregnancy. This implies the production not only of fertilizable haploid ova (and embryos) capable of developing into a baby, but also a receptive endometrium to nourish implantation of one or more embryos (Cohen *et al.* 1984; Rogers *et al.* 1986). In our opinion, only IVF cycles that result in a pregnancy should be used in any analysis of desirable LH levels in the preceding follicular phase.

Our study therefore was: (1) to determine a normal range for serum LH during standard follicular stimulation for IVF from 102 consecutive IVF conception cycles; (2) to determine whether serum LH levels are normally distributed; and (3) to use this range to test whether abnormally elevated serum LH concentrations were associated with decreased fertilization and pregnancy rates.

Subjects and methods

The Monash University IVF–Embryo Transfer (ET) Program has been described previously (Wood & Trounson 1984; Wood *et al.* 1985).

The women in the present study constituted part of a total group of 331 IVF conception cycles treated at our hospital between June 1980 and August 1985 A variety of ovarian stimulation regimens was used during that time. Of 299 conception cycles in which daily LH values were available, 270 cycles were stimulated by various combinations of clomiphene citrate (CC; Merell-Dow, Sydney, Australia) and human menopausal gonadotrophin (hMG; Serono, Melbourne, Australia). Of these IVF conception cycles, 102 consecutive cycles were stimulated by our standard regimen of clomiphene and hMG. Each woman had one conception cycle. The LH range so derived was then applied to a consecutive series of 596 women treated with this standard regimen of clomiphene–hMG for IVF in 1986.

Standard regimen of clomiphene/hMG stimulation

Clomiphene citrate (100 mg/day for 5 days) was begun 10 days before the calculated midpoint of the cycle. This likely day of the expected midcycle LH surge is based on the woman's previous six menstrual cycle lengths as reported by MacIntosh *et al.* (1980). This method derives linear regression equations to predict the day of LH surge and its 95% confidence limits. Treatment with hMG (150 iu/day) was started 1 day after the start of clomiphene and continued until the serum oestradiol (E_2) level was 1600–3200 pmol/l and steadily rising. The duration and daily dosage of hMG were often adjusted between 0 and 150 iu/day depending on the individual response as judged by serum E_2 and ovarian ultrasound determinations. The timing of the blood sampling, human chorionic gonadotrophin (hCG) injection, oocyte collection technique and other IVF–ET methods have been described previously (Wood & Trounson 1984, Wood *et al.* 1985).

In brief, when the serum E_2 concentration at 08.00 hours was approximately 3200 pmol/l, blood samples were taken at 08.00, 14.00 and 21 00 hours for serum E_2, LH and progesterone determinations. Treatment continued until serum E_2 concentrations reached approximately 1600 pmol/l for each 18 mm follicle, provided the serum progesterone concentrations remained below 7 nmol/l. If a surge in serum LH had not occurred within 36 h of the predicted day of the LH surge, 5000 iu hCG were administered and oocytes were aspirated 28–36 h later.

Hormone assays

All serum samples obtained at 08.00 hours were assayed for LH using a specific radioimmunoassay (RIA; Diagnostics Products Corp., Los

Angeles, CA, USA). This is a modified version using 100 μl serum sample and a 1·5 h incubation time, double antibody liquid phase ^{125}I-labelled RIA. Intra- and interassay coefficients of variation for this LH RIA at 20 iu/l were 4·2 and 4·0% respectively. The least detectable serum LH concentration was 2·7 iu/l.

Statistical analysis

Previous reports used the menstrual day or the day of hCG administration as the reference day for analysis of ovarian stimulation (Stanger & Yovich 1985; Howles *et al.* 1986). We consider that these timings are not ideal, since menstrual cycle length will vary between patients and the appropriate time for hCG administration is usually a subjective clinical decision. To try to induce multiple follicle growth, we begin clomiphene/hMG treatment 10 days before the predicted day of LH surge (Trounson & Calabrese 1984), midpoint of the cycle (MP) We have chosen to describe the range of serum LH values in our women with successful outcome of IVF who received clomiphene/hMG from this day. The range of serum LH results is, therefore, a prospective analysis.

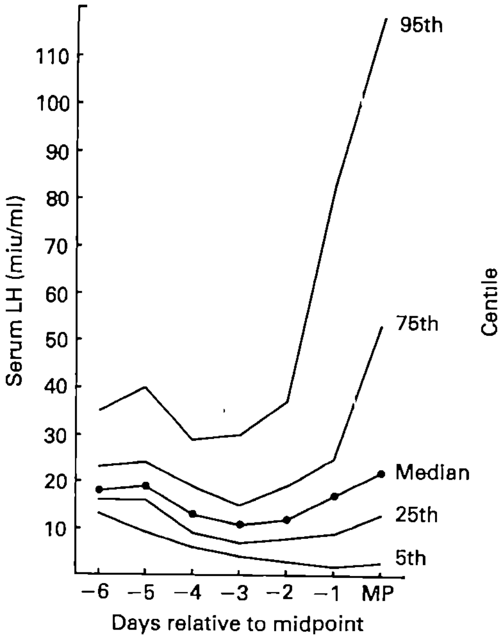

Fig. 1. Daily median serum luteinizing hormone (LH) concentrations in 102 consecutive IVF conception cycles in women treated with 100 mg clomiphene for 5 days beginning 10 days before the calculated midpoint of the cycle (MP) and with 150 iu hMG starting the day after clomiphene. The 5th, 25th, 75th and 95th centile values are also shown

Results

Serum LH values in these 102 IVF conception cycles had a skewed (non-Gaussian) distribution (Fig. 1). The median serum LH concentration, determined 5 days before the anticipated midpoint, was 20 miu/ml. The 75th and 95th centile levels became increasingly skewed as they approached the anticipated midpoint.

Of the 596 subsequent consecutive women undergoing IVF, 28 (4·7%) had a serum LH concentration above the 95th centile on ≥3 days of the IVF treatment cycle between MP−6 and MP−2, and 127 women (21·3%) had a serum LH value above the 75th centile on ≥3 days of IVF treatment.

The median number of oocytes retrieved from patients with serum LH concentrations above or below the 95th centile was six and four while the median number of oocytes fertilized was three and three respectively (P>0·05; Kolmogorov–Smirnov test). Using the 75th centile of serum LH concentrations as a discriminator, the median number of oocytes retrieved was four and five and the median number of ooctyes fertilized was three and three respectively (P>0·05).

Table 1 shows the fertilization and pregnancy rates for these women using either the 95th or the 75th centile as a discriminator. Neither the fertilization rate nor the pregnancy rate per embryo transfer procedure was statistically significantly reduced in the women with serum LH level > the 95th or >75th centile on ≥3 days of IVF treatment (P>0·10).

Discussion

Our findings indicate that follicular-phase serum LH values do not predict fertilization rate or clinical outcome after IVF, in contrast to previous reports of reduced fertilization rates (Stanger & Yovich 1985) or outcome (Howles *et al.* 1985). The role of LH in early pregnancy loss in women with polycystic ovary syndrome undergoing IVF is a different issue and was not addressed in our study (Abdulwahid *et al.* 1985). Many pregnancies in our IVF programme would not have occurred if attempts at oocyte retrieval

Table 1. Fertilization and pregnancy rates per embryo transfer procedure according to follicular-phase serum luteinizing hormone (LH) concentration*

	Serum LH concentration centile				All women treated in 1986*
	>95th (*n*=28)	<95th (*n*=568)	>75th (*n*=127)	<75th (*n*=469)	(*n*=845)
Median no. oocytes retrieved	6	4	4	5	
Median no. oocytes fertilized	3	3	3	3	
Fertilization rate (%)	63·1	67·5	68·2	67·2	65·2
Pregnancy rate/ transfer (%)	14·3	13·7	11·8	13·4	16·5

* The rates for all women treated in 1986 are shown for comparison.

had been cancelled because of high serum LH values.

The LH concentrations in our study were measured by a polyclonal radioimmunoassay. Earlier reports (Stanger & Yovich 1985; Howles *et al.* 1986) suggesting that serum or urinary LH values could predict fertilization or pregnancy rates after IVF also used radioimmunoassayable LH determinations. The percentage of non-bioactive LH which can be measured in a given radioimmunoassay is variable, as is the content of bioactive LH in commercial gonadotrophin preparations (Romani *et al.* 1977). Although the LH radioimmunoassay used in our study has been shown to correlate with an LH bioassay (unpublished observations), this agreement has not always been found with other LH radioimmunoassays (Meldrum *et al.* 1984; DeFazio *et al.* 1985). The number of immunologically active LH epitopes which are not biologically active could make interpretation of urinary LH concentrations in women undergoing IVF especially difficult.

Recent information indicates that follicle-stimulating hormone (FSH) alone is predominant for follicular development in women and that very small concentrations of LH are necessary for satisfactory folliculogenesis in the human (Jones *et al.* 1984). Satisfactory IVF folliculogenesis with highly purified FSH preparations diminishes the case that the precise level of serum LH is critically important for human follicle growth and normal fertility (Jones 1985). Our study indicates that measurement of serum LH during ovulation induction for IVF is not clinically useful in patient management in that follicular-phase LH values do not predict fertilization rate or clinical outcome.

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Correlation of ultrasound findings and endometrial histopathology in postmenopausal women

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Summary. Comparison of ultrasound scan and histology of the endometrium was made in 90 postmenopausal women. Of these, 63 women had postmenopausal bleeding (group A) and 27 had had no bleeding (group B). Sensitivity of ultrasound to diagnose endometrial pathology was 91%, and all endometrial carcinomas, hyperplasias and pyometra were diagnosed by ultrasound. In 10 premenopausal women (group C), who had a hysterectomy for cervical intraepithelial neoplasia, the ultrasound measurements of the endometrial wall thickness were within 1 mm of the actual thickness, as measured in the fresh unfixed specimen with a ruler. This preliminary study has shown that a normal ultrasound appearance of the endometrium in postmenopausal women reliably excludes significant endometrial pathology. Also, changes in the thickness and texture of the endometrium detected by ultrasound correlated with subsequent pathological findings.

Approximately 5% of women attending gynaecological outpatient departments in the UK present with postmenopausal bleeding. Concern to exclude cancer means that if a definite cause is not immediately evident from the history and clinical examination then diagnostic curettage is usually performed

Developments in the resolution of soft tissue interfaces by real-time ultrasound scanners enables study of the endometrium. This prospective pilot study was designed to test the hypothesis that ultrasound scanning could be used diagnostically and as a screening investigation to detect endometrial carcinoma and other endometrial pathology in postmenopausal women.

Patients and methods

The study included 100 women who had an ultrasound examination of the endometrium before dilatation and curettage or hysterectomy at Whiston Hospital between January and December 1987. All gave informed consent, and local ethical approval was obtained.

The women were divided into three groups. One group (group A) included 63 women between 50 and 76 years of age, who had presented with postmenopausal bleeding, defined as vaginal bleeding at least 1 year after the cessation of menses; none was receiving hormone replacement therapy. They were all scheduled to have a curettage although 33 women had medical problems, mainly cardiovascular or respiratory, and in four the operation had to be postponed for further medical treatment The second group (group B) included 27 postmenopausal women, between 53 and 81

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Table 1. Clinical diagnosis and operations in 27 asymptomatic postmenopausal patients (group B)

Clinical diagnosis	*n*	Operation	*n*
Uterine prolapse	18	Vag. hyst	15
		Repair and D & C	3
Cervical dysplasia	1	TAH & BSO	5
Uterine fibroids	2		
Ovarian mass	2		
Cervical polyp	4	D & C and cervical polypectomy	4

D & C, Dilatation and curettage, Vag. hyst , vaginal hysterectomy, TAH & BSO, total abdominal hysterectomy and bilateral salpingo-oophcrectomy

years of age, who had not had postmenopausal bleeding. Their clinical diagnoses and operations performed are listed in Table 1.

To assess the accuracy of our ultrasound measurements of the endometrial thickness, we included the third group (group C) comprising 10 women between 28 and 46 years of age who were due to have hysterectomy as treatment for cervical intraepithelial neoplasia.

Ultrasound examinations were performed with a SIEMENS Sonoline SL-2 combined Linear and Sector Real-Time Scanner using a 3·5-MHz probe and a technique similar to that described by Fleischer *et al.* (1986). The thickness of the endometrium was taken from the proximal and distal interfaces between the highly reflective and surrounding poorly reflective layers and measured in both longitudinal and transverse sections of the uterus. The average endometrial thickness was then calculated. The actual thickness of each endometrial wall was taken as half of the total linear distance measured, assuming there was no significant separation of the most superficial layers of the endometrium by intracavity fluid. Each examination took between 5 and 10 min.

In those women in groups B and C who had a hysterectomy, the fresh unfixed specimen was examined generally within 1 h after operation. The pathologists were always unaware of the ultrasound measurements. The uterus was measured externally and then bisected in the sagittal plane. The actual thickness of the endometrium of both anterior and posterior walls in the mid portion of the body was measured with a ruler. Lesions were described and similarly measured. In all patients the ultrasound findings were compared with the operative and pathological results.

Results

Group C

In all 10 women the ultrasound measurements of the endometrial wall thickness and the measurements made with a ruler on the hysterectomy specimen were within 1 mm of each other (within 0·5 mm in nine uteri). The average endometrial thickness was 6·7 mm (range 3·7–13 mm) as measured with a ruler.

Group B

The findings in the 27 women in group B are shown in Table 2. The dimensions of the uterus were small, consistent with the atrophic postmenopausal uterus. The uterine cavity appeared on ultrasound as a linear central echo oriented in the cranio-caudal axis (Fig. 1). The ultrasound measurements of endometrial thickness ranged from 1·9 to 4 mm (mean 2·34) in 21 patients. Hysterectomy was done in 16 patients, and the endometrial thicknesses measured by

Table 2. Ultrasound and histological findings in 27 asymptomatic postmenopausal patients (group B)

Ultrasound findings			
Diagnosis	*n*	Mean endometrial thickness (mm)	Histological findings
PM uterus	21	2 34	Inactive endometrium*
PM uterus+endometrial polyps	2	6·6	Benign endometrial polyps
PM uterus+endocervical polyp	1	10·0	Endocervical polyp
Others	3	—	See text

*The mean endometrial thickness of 16 hysterectomy specimens was 2·48 mm
PM, Postmenopausal.

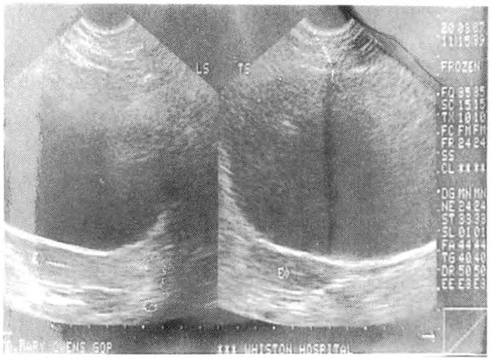

Fig. 1. Sonograph showing a normal postmenopausal uterus in both longitudinal and transverse sections (LS and TS) with a linear central echo endometrium (E).

ruler in the unfixed specimens ranged from 1·7 to 4 mm (mean 2·48). Dilatation and curettage was performed in five women, and in two of them ectocervical polyps were also removed. Histology from the curettings or hysterectomy specimen showed an inactive normal postmenopausal type endometrium. There was no statistically significant difference between the ultrasound and linear measurements of the endometrial thickness (the difference was <0·5 mm in all cases). In two women ultrasound showed a well-defined thick endometrium with increased reflectivity surrounded by a symmetrical area of low amplitude echoes with the cranial part of the uterine axis thinner than the caudal part. These were interpreted as simple endometrial polyps and this was confirmed by the histology. In one woman the endometrial thickness was far greater in the caudal part of the uterine axis and an endocervical polyp measuring 13×8×7 mm was subsequently removed. Ultrasound assessment of the endometrium was difficult in one woman with procedentia, even after manual replacement of the uterus. Histology confirmed an inactive endometrium with 2 mm thickness. In two patients ultrasonography demonstrated fibroids within the uterus. One patient had multiple fibroids distorting the uterine cavity, the other had a retroflexed uterus with a calcified fibroid, an endocervical polyp, and a left ovarian cyst which had not been detected by clinical examination and was shown to be a serous cystadenoma on histology.

Group A

Table 3 shows the ultrasound and histological findings in group A (women with postmenopausal bleeding). In 37 patients ultrasound showed a normal postmenopausal uterus and curettage removed inactive postmenopausal type normal endometrium or no material. Ectocervical polyps were removed from five patients.

Simple polyps were found in 10 patients. Ultrasound examination predicted endometrial polyps in seven, but in the other three, ultrasound revealed only a thickened endometrium of normal texture, not specifically diagnostic of the endometrial polyps which were removed subsequently.

In three patients ultrasound showed a well-defined, thick and highly reflective layer occupying the whole of the endometrial cavity and surrounded by a symmetrical poorly reflective zone (Fig. 2). Histology revealed simple hyperplasia (cystic glandular hyperplasia) in two women and

Table 3. Ultrasound and histological findings in 63 women with postmenopausal bleeding (group A)

Ultrasound findings				
Diagnosis	*n*	Endometrial thickness* (mm)	Histological findings of curettage	*n*
PM uterus	37	3·2 (1·9–4·5)	No material	26
			Inactive endometrium	11
PM uterus+endometrial polyp	10	8·3 (4·8–15)	Benign endometrial polyps	10
PM uterus+endocervical polyp	2	5·3, 7·9	Benign cervical polyps	2
Hyperplasia	3	20 (17–26)	Simple hyperplasia	2
			Atypical hyperplasia	1
Carcinoma	7	24·4 (11·5–38)	Endometrial carcinoma	7
Intracavity fluid	2	13, 40	Pyometra	2
Others	2		See text	

*Values are given as means (range) where appropriate.
PM, Postmenopausal.

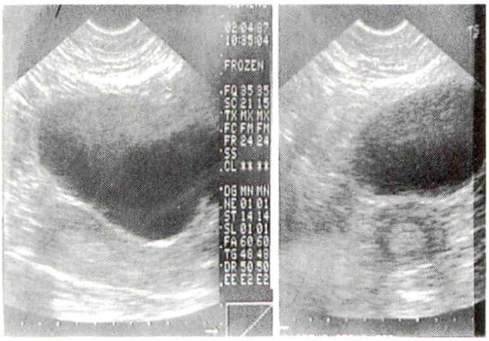

Fig. 2. Sonograph showing a postmenopausal uterus with highly reflective endometrial hyperplasia surrounded by a symmetrical zone of low amplitude echoes. LS and TS.

mild atypical hyperplasia (grade 1 intra-endometrial neoplasia) in one.

In seven women ultrasound correctly predicted carcinoma of the endometrium. The lesion appeared as an irregular, thickened, highly reflective area of endometrial lining with loss of the surrounding symmetrical area of low amplitude echoes (Fig. 3). In addition, two scans showed scattered areas of decreased reflectivity amid the increased reflective endometrial lining. Histology confirmed endometrial adenocarcinoma in all seven women which was proved to be invasive in the subsequent hysterectomy specimens. In one the lesion extended to the cervix. There was good correlation between the ultrasound measurement of the cavity length (external os to fundal endometrium) and that measured by a uterine sound at curettage. In four patients the cavity length was short, between 52 and 72 mm, and in three patients it was long, between 93 and 113 mm.

In two patients ultrasound showed an echo-free and irregularly widened uterine cavity (Fig. 4); curettage showed a pyometra in both. The cervices were clinically abnormal, and biopsies showed squamous-cell carcinoma which was invasive in one case and *in situ* in the other.

A 69-year-old woman had recurrent episodes of postmenopausal bleeding with no curettings obtained. Clinical examination showed a uterus equivalent in size to 14 weeks gestation. Ultrasound showed a myometrial lesion 15×11×10 cm distorting the uterine cavity. Unlike the uterine fibroids seen in two women in group B, the texture was heterogeneous with areas of moderate reflectivity and others of high-level echoes associated with distal acoustical shadowing suggesting calcific degeneration. Echo-free foci were also present indicating necrosis. Sarcoma was therefore suspected, and histology on the hysterectomy showed a leiomyosarcoma. In one further patient with a normal uterus on ultrasound, the bladder wall was thickened and subsequent cystoscopy and biopsy showed granulation tissue and inflammatory exudate.

Figure 5 illustrates the relation between the average ultrasound endometrial thickness and the histological findings in 85 postmenopausal women (groups A and B). In the 58 patients with normal ultrasound where histology had shown an inactive normal postmenopausal endometrium or where no curettings were obtained the ultrasound-measured endometrial thickness ranged between 1·9 and 4·5 mm. These results indicate that if the endometrial thickness is <5 mm throughout the whole cavity in postmenopausal women, the endometrium will be atrophic and probably inactive. If there is either focal or generalized endometrial thickness >5 mm then some pathology should be expected. Endometrial polyps were shown histologically in 12 women, in nine of them this was diagnosed by ultrasound but in the other three the ultrasound features were not sufficiently specific for a definite diagnosis.

The sensitivity of ultrasound to detect endometrial pathology in a postmenopausal uterus was 91%. Ultrasound correctly predicted all endometrial carcinomas, hyperplasia, and pyometra. The overall specificity of this test to exclude any endometrial pathology was 100%.

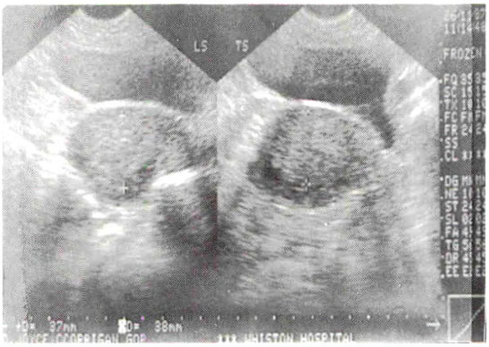

Fig. 3. Sonograph showing endometrial carcinoma in postmenopausal uterus (between asterisks) with irregular thick endometrium of increased reflectivity and disruption of the ultrasound subendometrial halo. LS and TS.

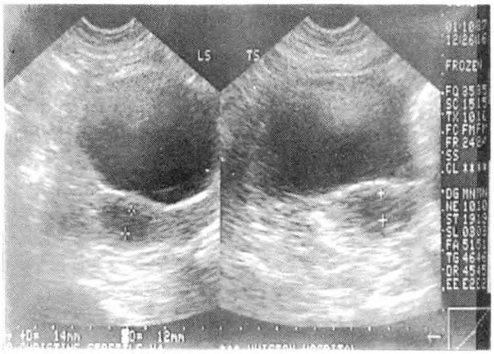

Fig. 4. Sonograph showing a postmenopausal uterus with an echo-free and irregularly widened uterine cavity (between asterisks) indicating intracavity fluid. LS and TS.

Discussion

Whilst the endometrium can be demonstrated in both longitudinal and transverse scans of the uterus, it is best delineated in the longitudinal axis as a greater proportion is included. Slight angulation and rotation of the transducer aids visibility. It was noted that in the longitudinal section the postmenopausal endometrium may not appear as a continuous line in every patient and occasionally only part may be seen. Therefore, ultrasonically the average thickness in both longitudinal and transverse sections, but not including the surrounding low amplitude echo layer, was taken as accurate representation of the endometrium. The nature of the low amplitude echo layer is believed possibly to represent a compacted muscle layer of the inner aspect of the myometrium (Symonds 1987) or to be due to a myometrial blood flow phenomenon (Lee *et al.* 1985). This study showed that this layer was symmetrical and intact in all normal postmenopausal uteri and also in all those with endometrial polyps, simple and atypical hyperplasia. It was absent or irregular in all uteri with invasive endometrial carcinoma. This finding is in agreement with Fleischer *et al.* (1987) who showed that myometrial invasion by carcinoma usually produces disruption of the ultrasound subendometrial halo.

Fleischer *et al.* (1988) stated that the endometrium in a postmenopausal woman should be thin (no more than 6–8 mm) and regular. Our findings are in agreement with this though with the equipment used the thickness of 5 mm appears to be a distinct cut-off point, below which all postmenopausal endometria were inactive and normal. In all women with an endometrial thickness above 5 mm, whether focal or the whole endometrium, the uteri were shown histologically to be abnormal.

We recommend that all women with postmenopausal bleeding where the cause is not immediately obvious should have an ultrasound examination. If the endometrial thickness is uniformly <5 mm a curettage is not necessary and other non-endometrial causes for the bleeding should be investigated. Where ultrasound shows focal or generalized thickening of the endometrium over 5 mm, a tissue diagnosis should be obtained.

Although three of our patients had endometrial polyps which were not specifically diagnosed by the abnormal ultrasound findings, no polyps were misdiagnosed as hyperplasia or neoplasia. In all ultrasound-predicted endometrial polyps, tissue diagnosis is advised not only because the numbers of patients in this study were small but because some hyperplasias, especially atypical hyperplasia (intraendometrial neoplasia), can be focal and not diffuse. Also, Pettersson *et al.* (1985) reported that endometrial polyps are associated with a threefold increased risk for endometrial carcinoma.

We recommend the routine use of ultrasound for women with postmenopausal bleeding, it is a simple non-invasive technique and highly acceptable to the patients. Where the endometrium is ultrasonically normal the woman will be spared an unnecessary operation, an important matter in this age group. In those patients

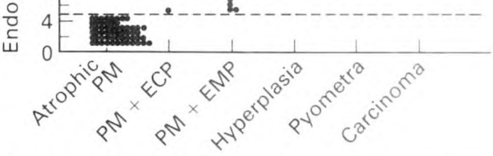

Fig. 5. Relation between endometrial thickness measured by ultrasound and histological findings in 85 postmenopausal women. The dashed line shows the cut-off level of 5 mm for abnormal findings. PM, Postmenopausal uterus; ECP, endocervical polyp; EMP, endometrial polyp.

shown by ultrasound to have an abnormal endometrium, a pre-operative diagnosis can be made with reliability in cases of invasive endometrial carcinoma. Endometrial ultrasound is eminently suitable for use as a screening procedure and we consider it should be included in those programmes using ultrasound to screen for ovarian neoplasms.

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Vulval intraepithelial neoplasia—management and outcome

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Summary. Forty-six patients with a primary diagnosis of vulval intraepithelial neoplasia (VIN) have been managed over a 10-year period. The prevalence of VIN has increased and the age at presentation has decreased over the last decade; 59% of our patients had histological evidence of human papillomavirus infection. Pruritis was the commonest symptom at presentation (59%). Of the 46 patients 44 were treated by laser skinning vulvectomy, local excision or simple vulvectomy. Symptomatic relief was best achieved by local excision. Clinical and definitive relapse occurred more often in the laser-treated group. The median time to relapse was 38 months in the laser-treated group and 74 months in the surgically treated group (excision and simple vulvectomy). Two patients have not been treated and their disease has not progressed. The carbon dioxide laser almost certainly has a role in conservative management and although our data possibly do not reflect its full potential they demonstrate a need for a controlled prospective study.

Intraepithelial neoplasia of the vulva (VIN) is diagnosed far less frequently than its cervical counterpart, yet once a diagnosis is made the situation is much more problematic for the clinician. VIN is being detected more often (Boutselis 1972; Buscema *et al.* 1980), and whilst this may be an observational rather than real change in incidence, more patients require management. This disease is being reported more frequently in young women (Woodruff *et al.* 1973; Buscema *et al.* 1980) and this has resulted in a desire to adopt less radical approaches to treatment in order to preserve structure and function of the vulva.

In the mid-1970s the carbon dioxide laser was introduced into gynaecology primarily to treat pre-invasive disease of the cervix. It soon became apparent that the precisely controllable destructive ability of the laser might be successfully applied to the eradication of VIN and this use has been reported (Reid 1985; Baggish & Dorsey 1981; Ferenczy 1983).

We have increasingly employed laser vaporization as a means of management since 1978 and this review summarizes a 10-year experience of this treatment and of others at our institution.

Patients and methods

The case records of 46 patients who had been diagnosed as having VIN at the Birmingham and

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Midland Hospital for Women over a 10-year period (1 January 1978 to 31 December 1987) were reviewed. The pathological specimens have all been reviewed by one of us (T.P.R.) and classified according to the most recent recommendations by the International Society for the Study of Vulvar Disease (1986); the reviewed diagnoses are used in the analysis.

Patient demographic information, clinical presentation and clinical features along with management and follow-up data have all been transcribed from the case notes. Most were followed up in colposcopy clinics, although in the early part of the series some patients were reviewed in general gynaecology clinics. No patients have been lost to follow-up.

Relapsed disease has been classified as symptomatic (if the patient's original symptoms recurred), clinical (if the presenting macroscopic features recurred), or definitive (if post-treatment biopsies confirmed persistent VIN).

Results

Occurrence and age

The median age was 43 years (range 17–80 years). In the first 5 years of the study (15 patients) the median age was 59 years whereas in the latter half of the study (31 patients) this was 35 years. This trend toward younger patients is reflected in the overall analysis where 29 (63%) were noted to be <50 years of age. The peak prevalence was in the fourth decade accounting for 19 (41%) of cases; 23 women were premenopausal and 13 postmenopausal, 10 had undergone previous hysterectomy

Symptoms

The most common presenting symptom was pruritis (27 patients (59%)). Other common presenting symptoms were vulval pain in 16 (35%), warts in 12 (26%) and vaginal discharge in 7 (15%). Other infrequent symptoms were vulval swelling in two patients, abnormal vaginal bleeding in two patients, recurrent candidiasis in one patient, and vulval discolouration (erythema) in one patient Often patients had two or more symptoms. The median duration of symptoms was 22 months (range 0·5–120 months).

Clinical features

In 41 patients the initial assessment included colposcopic examination of the lower genital tract. Varied appearances were noted. Sixteen patients had lesions suggestive of warts (raised and papular) and 11 had leukoplakia. Six had a diffuse erythematous lesion suggestive of an inflammatory process whilst four had raised irregular lesions suspicious of malignancy, three patients had a vulval ulcer. In the remaining six patients vulval biopsy, and hence confirmation of VIN, was prompted by mild colposcopic changes (diffuse erythema and acetowhitening). One patient was totally asymptomatic and had minor skin changes noted whilst being investigated for abnormal cytology. In 22 patients (49%) the lesions were multifocal and in 20 unifocal. Three patients had lesions described as being confluent.

Coexistent or previous disease

Of the 46 patients 19 (41%) had previously had at least one abnormal cervical smear and 20 (43%) had concurrent or previous cervical intraepithelial neoplasia. In addition, three patients had vaginal intraepithelial neoplasia.

Diagnosis

Diagnosis was by single biopsy in 30 and multiple biopsy in 13 patients. In three patients simple vulvectomy was performed as a primary procedure. All but six patients were biopsied under general anaesthesia although latterly our practice has been to use a Keyes punch biopsy knife with local anaesthesia. Of the 46 patients 30 (65%) had VIN 3, 7 (15%) VIN 2, and 9 (20%) VIN 1; 27 of the biopsies (59%) showed associated koilocytosis.

Management

Overall, 21 patients were treated initially by laser skinning vulvectomy, 14 had local excision and nine patients were treated by simple vulvectomy. Multifocal disease was present in 22 patients, unifocal in 20, confluent in three and unknown extent in one. Those with more extensive disease were treated by simple vulvectomy or laser and those with less had local excision. Those treated with laser tended to be younger (average age 36 years) than those treated with local excision (average age 51 years) or simple vulvectomy (average age 58 years). Two patients had no definitive treatment but have been closely followed up after diagnostic biopsy. Patients undergoing treatment were counselled before surgery. Bowel preparation using mannitol 10% 500 ml was employed in the presence of perianal disease. Laser skinning vulvectomy was undertaken by experienced personnel using a carbon dioxide laser in superpulse or chopped mode. Affected areas were lasered to the third surgical plane using the visual landmark of coarse collagen fibres, re-epithelialization occurring from normal keratinocytes in the underlying appendages (Reid 1985). A Foley or suprapubic catheter was used if micturition soiling was a possibility. Postoperatively, paraffin gauze was applied to prevent the skin edges sticking together. This dressing was removed within 24 h. The treated area was irrigated with normal saline, dried with a hairdrier, and silver sulphadiazine cream applied at least twice daily. Care was taken to prevent labial adhesions. Postoperative pain was maximal 2–4 days after laser therapy, coinciding with vulval oedema. Paracetamol or dihydrocodeine was used for pain relief, buprenorphine occasionally being required. Local care of the vulva was continued at home. Complete healing occurred in 3–6 weeks. Three of the patients treated by laser skinning vulvectomy developed labial fusions which were managed by excision using laser under general anaesthetic. A further patient treated by laser, who had anal and perianal disease subsequently developed an incompetent anus that required surgical correction. One patient developed a deep vein thrombosis and pulmonary embolism after simple vulvectomy. The patient made a full recovery after anticoagulation therapy.

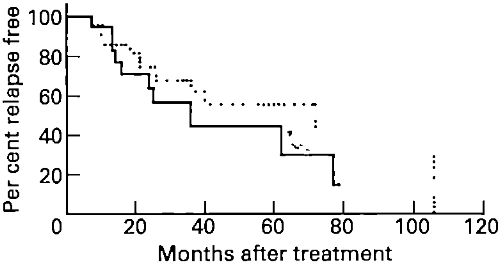

Fig. 1. Life-table of definitive relapse after laser (———) or surgical (. ..) excision of VIN. Laser group· total $n=21$, relapse $n=10$; surgery group: total $n=23$, relapse $n=10$.

Follow-up

Most patients were followed in the colposcopy clinic; mean follow-up time was 35 months but the timing schedule was variable. Overall, 52% of patients achieved full symptomatic relief after treatment, seven of 21 (33%) had symptomatic relief after laser vaporization, and 10 of 14 (71%) experienced relief with local excision. Four of the nine patients treated by simple vulvectomy (44%) also experienced symptomatic relief. Follow-up examination (by colposcopy) demonstrated that clinical stigmata of disease persisted in 21 patients. This included 11 of the 21 patients treated by laser skinning vulvectomy and three of 14 managed by local excision. Four patients had persistent signs of disease after simple vulvectomy. Persistent disease was also recognized and rebiopsied in the two untreated patients.

Further histological material was submitted in 21 patients with persisting signs of disease. In 17 persistent VIN was confirmed, in three early invasive disease was noted. In one no evidence of preinvasive or invasive disease was found, leaving a total of 20 histologically confirmed relapses. The median time to relapse in the laser-treated group was 38 months and 74 months in the surgically treated group (excision and simple vulvectomy). Time to relapse in the two treatment groups is demonstrated in Fig. 1. Neither of the two untreated patients had evidence of invasive disease.

Further treatment

Nineteen patients with persisting clinical signs of disease and two who had persistent pruritis (in the absence of clinical signs) were treated by either laser or excisional techniques. Choice of further treatment did not depend on the type of first-line treatment.

Discussion

Although uncommon, VIN presents a considerable challenge to the clinician, not only because of an apparent increase in incidence, but also because the disease is more frequently recognized in younger women (Hensen & Tarone

1977; Friedrich *et al.* 1980; Bernstein *et al.* 1983; Wolcott & Gallup 1984). Both of these phenomena have been noted in our analysis, but there is little doubt that an increased diagnostic awareness has occurred in our unit since the introduction of colposcopy.

It was of interest to note that 59% of our patients had histological signs suggesting human papillomavirus (HPV) infection. Much has been written about the possible aetiological role of HPV in this condition (Crum *et al.* 1982; Rastkar *et al.* 1982; Kennedy *et al.* 1987) and whilst it would be premature to suggest that these viruses are oncogenic in terms of vulval disease they are being recognized more frequently. Such circumstantial evidence will demand close assessment in the future. Vulval warts are commonly found in association with VIN, but it is not possible to say whether this represents an unrelated HPV infection or whether there is a common aetiology. Indeed, it is often quite difficult histologically to differentiate the lesser grades of VIN from HPV infection.

Regardless of the aetiology, the clinical problems presented by VIN must be faced. Because of the similarities between CIN and VIN, there is a risk of assuming that what is relevant in the management of the former applies to the latter. CIN is an asymptomatic disease detected as a result of screening and it is generally agreed that all women with CIN should be treated because of the significant risk of progression to invasive disease. In contrast, VIN is commonly diagnosed because of vulval symptoms, although the advent of vulval examination with the colposcope can lead to the diagnosis of asymptomatic VIN in women with CIN. It is this latter group which poses the real management dilemma for the clinician. Should asymptomatic VIN be treated, and if so, why? One must caution against seeking too many parallels with CIN. Indeed, progression of VIN to invasive cancer would appear to be uncommon (Friedrich *et al.* 1980; Choo 1982; Woodruff *et al.* 1973; Jones & McLean 1986) except in the very elderly or immunosuppressed patients (Buscema *et al.* 1980). Futhermore, there is little evidence to suggest that the risk of malignant progression is related to grade of severity of VIN.

Over the past 20 years the management of VIN has become less radical. Various approaches have been reported including vulvectomy (Parry Jones 1976), skinning vulvectomy (Rutledge & Sinclair 1968), wide local excision (Forney *et al.* 1977), topical 5-fluorouracil (Carson *et al.* 1976), di-nitro chlorobenzene (Weintraub & Lagasse 1973), cryosurgery (Forney *et al.* 1977), and vaporization using the carbon dioxide laser (Baggish & Dorsey 1981; Townsend *et al.* 1982; Wright & Davies 1987). The trend towards less radical treatment is partly because of the realization that there is a very small, although uncertain, risk of progression to invasive cancer, and partly because the disease is being diagnosed in younger women who wish to avoid mutilating surgery and thus preserve sexual function. The carbon dioxide laser has become a very popular instrument for the management of CIN. The same principles apply to the treatment of VIN using the laser. Pre-invasive disease must be confirmed and invasive disease must be excluded by thorough colposcopic assessment of the vulva with biopsy of any areas of abnormal epithelium. Under colposcopic control, the neoplastic tissue can be identified accurately and vaporized, thus preserving as much normal tissue as possible.

Success rates of up to 94% have been reported following a single treatment with the carbon dioxide laser (Baggish & Dorsey 1981; Townsend *et al.* 1982; Wright & Davies 1987). However, follow-up in these studies was limited. Our results were comparable when short-term follow-up was considered (Fig. 1), but when our group of patients was followed for longer periods the relapse rate was disappointingly high.

Whilst our series is not prospective, several pertinent points arise. Using symptomatic recurrence and biopsy confirmation, none of the methods proved wholly successful. Compared with other studies, our rather disappointing results after laser vaporization must be interpreted against the background of duration of the study. The new techniques and application of the carbon dioxide laser were poorly understood in the early part of this series and it is probable that depth of destruction was inadequate. VIN, regardless of degree, is always present in the basal layers of the epithelium. If the deepest rete ridges are not vaporized, it is likely that the disease will persist. Furthermore, even if the rete ridges are ablated adequately, residual disease may result because of the presence of neoplastic epithelium in the skin appendages deeper in the dermis. The apparent superiority of local excision may reflect case selection as this technique was more often applied to smaller unifocal lesions, rendering comparisons invalid The failure of simple vulvectomy to control disease in 5 of 9 patients may have been due to incomplete excision of disease.

One explanation for treatment failures lies in the field change theory in which the whole of the lower genital tract epithelium is at increased risk of neoplastic transformation. This is supported by our observations and those of other studies (Jones & McLean 1986; Bernstein *et al* 1983; Caglar *et al* 1982) which have shown that intraepithelial neoplasia of the cervix and vagina is frequently found in women with VIN The field theory is further supported by reports of intraepithelial neoplasia developing in a vulval skin graft (Cox *et al.* 1986) and in a neovagina (Lathorp *et al.* 1985) in women treated for in-situ disease of the lower genital tract. An equally plausible explanation for treatment failures is incomplete excision as this has been shown to be associated with an increased risk of recurrent disease (Wolcott & Gallup 1984). Multifocality and varying clinical characteristics are well described and it is possible that techniques currently employed to guide biopsy are inadequate.

We believe it is necessary to include symptomatic as well as biopsy proven failure because, in the final analysis, it is the control of symptoms that may well be of major import. Normal vulval skin shows a diploid pattern on flow cytometry, whereas VIN and squamous carcinoma of vulva are associated with aneuploidy (Evans *et al.* 1987). Whilst not wishing to ignore the potential of malignant transformation, the currently available data and regression of aneuploid lesions (Friedrich *et al.* 1980) suggest that the lesion is of low malignant potential in the majority of women. Further avenues of research must direct themselves at identifying that small group and define effective conservative measures at controlling the distressing symptoms frequently associated with VIN. The carbon dioxide laser has a role in the management and although our data possibly do not reflect its full potential they demonstrate a need for carefully controlled prospective assessment.

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Is it time for a reconsideration of the criteria for cone biopsy?

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Summary. Between August 1985 and November 1988, 475 laser cone biopsies were performed at the Regional Gynaecological Oncology Unit in Gateshead. Of these, 332 were performed for abnormal cervical cytology and unsatisfactory colposcopy. The negative cone rate in this group was 34%. In those with cytological abnormalities up to and including mild dyskaryosis the figure was 64% and there were no cases of invasive disease. In this group the authors have reconsidered the criteria for cone biopsy and suggested biopsy of the visible ectocervical lesion combined with endocervical curettage or brushing. Those with negative histology or cytological abnormalities less than moderate dyskaryosis should be managed conservatively.

Prior to the mid 1970s, before the widespread availability of colposcopy, women with abnormal cytology were usually only referred to the gynaecologist after two successive severely dyskaryotic smears. The reason for this management was that the only diagnostic/curative procedures available were either a knife cone biopsy or a hysterectomy with their potential complications. With the introduction of colposcopy most women with abnormal smears can now be managed successfully in the outpatient clinic; consequently women are being referred to the colposcopist with milder degrees of cytological abnormality. This trend toward increased referral has been strengthened by recent reports showing significant cervical intraepithelial neoplasia (CIN) in women with only mildly abnormal cervical smears (Soutter *et al.* 1986; Bolger & Lewis 1988).

In a minority of women presenting with abnormal cytology, colposcopy will be unsatisfactory because of failure to identify the endocervical limit of the transformation zone This proportion increases with age With the recent nationwide introduction of the cervical cytology call and recall system a large number of previously unscreened older women in the postmenopausal age group are now referred to the colposcopy clinic.

The currently accepted policy of management for those patients who do not have 'satisfactory colposcopy' (i.e. the entire limits of a colposcopic abnormality cannot be defined) involves diagnostic cone biopsy (Jordan 1980).

The objective of this study was to review the frequency of 'negative' cone biopsies in women referred for colposcopy with an abnormal smear and to determine how this could be reduced.

The review has led us to reconsider the broad criteria used in the decision to perform cone biopsy.

Subjects and methods

Between August 1985 and November 1988 a total of 475 laser cone biopsies was performed at the Regional Gynaecological Oncology Unit,

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Table 1. Relation between decision cytology and cone histology

Decision cytology	Cone histology Negative	HPV	CIN1	CIN2	CIN3	Micro-invasive carcinoma	Squamous cell carcinoma	Adeno-carcinoma *in situ*	Adeno-carcinoma	Total
Irregular	6		1		4					11
Mild dyskaryosis	33	1	2	1	13					50
Moderate dyskaryosis	51	3	4	1	67	2			2	130
Severe dyskaryosis	17		1	1	97	3	5	2	1	127
Abnormal endocervicals	3				4					7
Squamous cell carcinoma					1					1
Total	110	4	8	3	186	5	5	2	3	326

HPV, Human papillomavirus

Gateshead. Of the 475 patients 59 had had previous cervical biopsies; 44 had persistent abnormal smears with negative colposcopic findings 21 had lesions which were fully visible but were suspicious of early invasive disease; and 19 were performed for other indications. The remaining 332 were performed for abnormal cervical cytology and unsatisfactory colposcopy and these patients comprised the study group. Six of this group were excluded from the study, three because the laser cone biopsies were unreportable and three because not all relevant information was available.

The criteria for colposcopy referral in this series were the same as those described by Soutter (1989).

The smear result which precipitated the decision to perform a cone biopsy was termed the 'decision cytology'. Patients emanated from a number of districts each with their own cytology services. It is important to note that we have used the term 'irregular' to cover several minor cytological abnormalities including borderline changes and mild squamous atypia.

The cone biopsies were performed under general anaesthesia; most were day case procedures. A Coherent 451 Laser linked to a colposcope was used with a spot size of 1·5 mm at a focal length of 300 mm and a maximum power of 40 W. A skin hook or Allis's tissue forceps was used to manipulate the cone (Monaghan 1986; Soutter 1987). Haemostatic procedures such as the use of vasoconstrictor substances and lateral cervical sutures were not employed routinely.

A 'negative' cone was defined as one containing no evidence of dysplasia of the squamous or glandular epithelium, no human papillomavirus (HPV) infection and no evidence of invasive disease. Although it is accepted that the sensitivity of the pathologist to the presence of HPV may have varied over this time, only four cones were reported to show changes of HPV alone.

Results

Of the 326 cones 110 (34%) were reported as negative.

Table 1 shows the distribution of 'decision cytology' and the relation to cone histology. Of the 326 patients 61 (19%) had 'irregular' or mildly dyskaryotic smears. Of the 127 patients who had severely dyskaryotic smears 108 (85%) had CIN 3, adenocarcinoma *in situ* or invasive disease.

No patient with an 'irregular' or mildly dyskaryotic smear had invasive or microinvasive disease; however, the negative cone rate in this group was 64%.

Overall, 46% were ≥40 years of age with a mean age of 40·1 years. The mean age of those with negative cones was 40·3 years and of those with histological abnormality was 39·9 years.

In 157 patients the length of the cone biopsy was recorded: 61% had a cone length of ≥20 mm with a mean length of 21·9 mm. The mean length of the negative cones was 22 mm and those with histological abnormality was 21·8 mm.

Of the 13 cones diagnosed histologically to be invasive only four were suspected on colposcopic examination.

Discussion

Although many papers have described the techniques and complications of cone biopsy, rarely has the problem of negative cones been addressed. Luesley *et al.* (1987) reported a negative cone rate of 17–19%, but there appeared to be a high percentage of patients with major cytological abnormalities, in contrast with our series. This difference reflects modern referral practice in a highly screened population. Recent papers describing laser cone biopsy do not comment satisfactorily on negative cone biopsies (Larsson *et al.* 1983; Fenton *et al.* 1986).

As screening of women becomes more comprehensive, it is inevitable that much minor cytological abnormality will be identified. When these minor abnormalities persist, referral to colposcopy clinics is recommended. Subsequently a number of such patients will be found to have unsatisfactory colposcopy and using standard criteria will have a cone biopsy. Our results show that many patients (64%) presenting in such a fashion will have negative cone biopsies.

Management of minor cytological abnormalities with unsatisfactory colposcopy

To reduce the occurrence of what may be an unnecessary procedure there are a number of techniques available. These include micro-colpo-hysteroscopy, endocervical curettage or endocervical brushing with colposcopically directed biopsy of the ectocervical lesion or simple cytological review.

The role of loop diathermy excision of the transformation zone has yet to be assessed in these patients.

Micro-colpo-hysteroscopy is useful only for the delineation of the abnormal epithelium and its upper limit in the endocervical canal. It has been used in conjunction with endocervical curettage to try to improve the yield of atypical epithelium (Baggish & Dorsey 1982).

Cytological review alone could delay treatment of those patients with cervical dysplasia. In the present series no patient with an irregular or mildly dyskaryotic smear would have been at risk of an invasive lesion being missed if this management had been employed. However, in 28% CIN 3 would have been untreated.

Biopsy of the visible ectocervical lesion may be combined with endocervical curettage or endocervical brushing to detect those patients with dysplasia. Patients showing moderate dyskaryosis or worse on endocervical brushing, or dysplasia on endocervical curettage or biopsy histology should subsequently have cone biopsy performed. Those with negative or mild abnormalities on endocervical brushing and negative histology could be followed with ecto- and endocervical cytology and colposcopy. If this policy were adopted it is possible that the negative cone biopsy rate of 35% could have been reduced, without missing any invasive cancer.

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Addisonian crisis in pregnancy. Case report

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Case report

A 35-year-old primigravid woman attended the antenatal clinic initially at 28 weeks. Before this she had been cared for by her family practitioner and the pregnancy was considered normal. Pernicious anaemia had been diagnosed 2 years earlier after a year of fatigue, anorexia, palpitations and diarrhoea. No associated autoimmune phenomena had been noted and the anaemia was adequately controlled with folate and vitamin B12 supplementation.

The patient was well at her first antenatal visit and routine antenatal blood investigations were within normal limits. Clinical examination and ultrasonography confirmed the presence of a normal 28-week fetus.

At 31 weeks the patient was admitted with symptoms and signs of a small placental abruption. She was haemodynamically stable (blood pressure 120/80 mmHg) and there were no signs of fetal distress. In view of her satisfactory condition and the relative immaturity of the fetus, conservative management was deemed appropriate. However, 8 h later the patient suddenly became lethargic, dehydrated, pyrexial (38°C), and her blood pressure fell to 90/50 mmHg. Oliguria ensued and this did not respond to the intravenous challenge of 300 ml Ringer's lactate. Electronic fetal heart rate tracings demonstrated a baseline tachycardia of 180–190 beats/min and absent short-term variability. The patient was not in labour, and despite a tense uterus, there was no vaginal bleeding. The fetus died during preparations for an emergency caesarean section.

Maternal condition remained unsatisfactory, and in consultation with intensive care staff, her condition was attributed to placental abruption and superimposed renal tract sepsis together with early phase septic shock. Central venous pressure monitoring and intravenous antibiotics were begun and labour was induced which culminated 4 h later in the spontaneous expulsion of a 1100 g fresh stillborn but otherwise normal male infant. The placenta was calcified, weighed 350 g, and a 20% marginal abruption was noted.

One hour postpartum the patient became hypothermic (rectal temperature 33°C), semi-comatose and hypotensive (blood pressure 70/0 mmHg). Haematological indices remained stable but there was a fall in serum sodium from 134 mEq/l to 125 mEq/l with a concomitant rise in serum potassium from 3·8 to 5·5 mEq/l. A simultaneous metabolic acidosis was noted (arterial blood gas analysis: pH 7·29 units; Pa,o_2 8·17 kPa; Std HCO_3 17·3 mmol/l and base excess 8·6 mmol/l) As a result of the hyponatraemia, hyperkalaemia and metabolic acidosis, a presumptive diagnosis of an acute adrenal crisis was made; blood was taken for a basal serum cortisol estimation (this proved to be 50 nmol/l: normal range 200–600 nmol/l) and 300 mg of hydrocortisone were given intravenously as a bolus. Isotonic saline was administered via a blood warmer and the patient placed on a warming blanket. The ambient temperature was raised to 28°C.

Within 4 h the patient was alert, normotensive and euthermic. Intravenous hydocortisone, 100 mg every 8 h, was continued for 24 h and the patient managed thereafter on oral dexamethasone, 1 mg per day. An ACTH stimulation test on the third postpartum day confirmed the diagnosis of Addison's disease; i.e. following the administration of 0·25 mg of

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synthetic corticotrophin intramuscularly the plasma cortisol level of 256 nmol/l only increased to 321 nmol/l 1 h after stimulation. There was no evidence of an associated polyglandular autoimmune failure, as autoantibody tests for ovary and thyroid were negative, but she did have parietal cell antibodies.

The patient was discharged on maintenance therapy of hydrocortisone, 20 mg in the morning and 10 mg at night.

The patient conceived again 3 months after delivery and remained well throughout her subsequent pregnancy. She was maintained on prepregnancy doses of hydrocortisone and 0·1 mg of fluorocortisone acetate during the antenatal period. She was delivered of a live healthy male infant with a birthweight of 3360 g at 39 weeks by lower-segment caesarean section (due to cephalopelvic disproportion). Intravenous hydrocortisone, 100 mg every 8 h, was administered intrapartum and for 24 h postpartum. Thereafter oral maintenance therapy was recommenced and there were no untoward postpartum sequelae.

Discussion

Primary hypoadrenalism (Addison's disease) is a rare complication of pregnancy and even if recognized and treated may be associated with fetal growth retardation (Osler 1962). Although the occurrence of intrauterine growth retardation in treated women with Addison's disease has been disputed, there is little disagreement as to the serious outcome for mother and fetus if the disease goes unrecognized during pregnancy (Hilden & Ronnike 1971; Gold 1983).

Diagnosis of Addison's disease in the non-pregnant patient is confirmed by a low cortisol level in either urine or plasma, and a lack of response to ACTH stimulation. In the pregnant patient with Addison's disease, cortisol levels may be within the normal non-pregnant range. Therefore the diagnosis must rest on the lack of rise in the plasma cortisol concentration after ACTH stimulation (Burrow 1982). Moreover, clinical manifestations of Addison's disease such as weakness, fatigue, increased pigmentation, weight loss, anorexia, hypoglycaemia and nervousness are common in normal pregnancy. Accordingly, the diagnosis may go unrecognized until acute adrenal crisis occurs (Finer *et al.* 1985; Burrow 1982).

Autoimmune adrenalitis is commonly associated with other autoimmune gland failures. Neufeld *et al.* (1980) classified the polyglandular syndromes into three subcategories. Genetic predisposition and the HLA B-8 haplotype are common to all three (Hadi *et al* 1983). Unfortunately, HLA-typing was not performed in this patient. Pregnancy has been reported in patients with the following polyglandular syndromes: (i) premature ovarian failure, Addison's disease and primary hypothyroidism (Finer *et al.* 1985); (ii) diabetes mellitus, Addison's disease and hypothyroidism (Poonai *et al.* 1979); (iii) Schmidt's syndrome which includes Addison's and thyroid insufficiency (Hadi *et al.* 1983; Drucker *et al.* 1984).

The patient with a preconceptual diagnosis of Addison's disease is managed by continuing prepregnancy regimens of hydrocortisone and fludrocortisone. Ordinarily, supplementation of prepregnancy steroid doses is not necessary during pregnancy. Significant postural hypotension during pregnancy indicates inadequate control of the Addisonian state, and the need to increase steroid doses. The stress of nausea and vomiting during the first trimester and infection at any stage of pregnancy must be vigorously managed. With the onset of labour, or for emergency surgery, the patient with Addison's disease requires intravenous hydrocortisone, 100 mg very 6–8 h, and this is continued postpartum for at least 24 h before restarting oral therapy (Gold 1983)

The patient with undiagnosed Addison's disease normally tolerates pregnancy but decompensates rapidly following the stress of labour and delivery. During pregnancy a significant antepartum haemorrhage, urinary tract infection or hyperemesis may precipitate an acute crisis. The crisis can occur spontaneously if basal cortisol levels are very low. Clinical features of the crises include nausea and vomiting, diarrhoea, flank pain, anorexia, inexplicable fever, extreme weakness, hypotension and vitiligo. Electrolyte anomalies include hyponatraemia, hyperkalaemia, mild azotaemia and metabolic acidosis. Hypoglycaemia is seldom a feature but, if present, is difficult to correct.

The major aim of therapy in the acute crisis is correction of the cortisol deficit. Emergency management includes intravenous hydrocortisone as a 100-mg bolus followed by a continuous infusion to give an additional 200 mg/24 h. Bolus doses every 6–8 h may be used but are less efficacious as the plasma half-life of cortisol is 90 min. In addition, 100 mg of cortisone acetate should be given intramuscularly every 12 h to cater for inadvertent discontinuance of intravenous therapy. Fludrocortisone is contraindicated in the acute situation as resultant salt and water retention may cause pulmonary oedema Salt and water deficits during the crisis are replaced by 3 litres of 5% dextrose saline per 24 h. Sodium bicarbonate is only given if the pH falls to less than 7·2. It is important to actively detect and treat concomitant infection. Hourly measurement of urine output is the most sensitive index of adequate therapy (Gilliland 1983).

The fetal outcome in patients with Addison's disease is generally good. Although initial reports indicated a prevalence of intrauterine growth retardation (Osler 1962), this has been disputed more recently (Hilden & Ronnike 1971). The fetal outcome in five cases reported in the literature since 1972 were as follows (i) one twin pregnancy intrauterine death at 28 weeks (Normington & Davies 1972); (ii) two growth-retarded infants (Drucker *et al* 1984); (iii) two appropriate-for-gestational-age infants (Hadi *et al.* 1983; Poonai *et al.* 1979).

Although maternal steroid therapy is teratogenic in animals, no teratogenicity has been demonstrated in human fetuses The frequency of cleft palate in infants exposed *in utero* to cortisone is reported as 1% and thus some consider it a weak teratogen Sudden withdrawal of cortiosteroids at birth has rarely been associated with neonatal haemorrhage, atrophy and necrosis (Tuchmann-Duplessis 1977)

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Deep and acute vulval ulceration. Case report

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Case report

A 28-year-old, married, West Indian woman presented to the Department of Genitourinary Medicine at St James's Hospital, Balham, in March 1986, complaining of vulval ulceration and pain.

Three weeks earlier she had noticed a slightly itchy 'lump' on the perineum. Local pessaries and cream, provided by the family doctor, gave no relief and 1 week later the lesion began to discharge pus. She then attended a local hospital casualty department and was treated with oral flucloxacillin (Floxapen) for 2 days with no improvement and finally she came to our department.

There was a past history of a similar, but milder, episode 7 years previously, 18 months after the birth of the first baby. The present attack began 9 months after the birth of the second child which was still breast-feeding, but no problems had occurred after a termination between these two pregnancies.

Both the patient and her husband had lived in Britain for many years and denied any other sexual contacts. He was asymptomatic with no signs of infection. She was taking an oral contraceptive, but no other drugs.

On examination, the patient had a large, gaping, painful ulcer with a purulent base and a well-defined, non-indurated edge, on the left lower labium majus extending from introitus to perineum, along the line of a previous episiotomy scar. The scar gave the appearance of having fallen apart (Fig 1). The inguinal lymph nodes were not tender or enlarged.

There were no signs of infection involving vaginal, cervical, perianal or oral mucous membranes and no other abnormalities were found elsewhere.

The blood count, liver function tests, serum urea and electrolytes and chest X-ray were normal; the ESR was 30 mm/h A test for antinuclear factor was negative, IgM was elevated at 3·4 g/l (normal 0·5–2·0), but paraproteins were not detected. Mantoux test 1 in 1000 was negative. Serological tests for syphilis, lymphogranuloma venereum, herpes simplex, *Chlamydia trachomatis*, hepatitis B surface antigen and autoantibodies were negative Viral, bacterial and fungal cultures, including those for *Haemophilus ducreyi* and acid fast bacilli, and dark field examination for spirochaetes were also negative from both genital tract and ulcer

While awaiting the results of initial tests, oral acyclovir (Zovirax) was added to the flucloxacillin therapy and she was admitted to the ward No improvement was noted after several days and a biopsy was taken The treatment was changed, first to oxytetracycline (Imperacin), then to doxycycline (Vibramycin) with metronidazole (Flagyl) and triamcinolone (Adcortyl) in orabase applied locally to the ulcer. Slight improvement occurred; the ulcer continued to discharge, but the edge began to granulate and became less tender.

The onset of menstruation produced a serious relapse. The ulcerated area became acutely painful with a rapidly spreading, eroded, undermined, necrotic edge, and a new, circular, white patch, approximately 1 cm in diameter, appeared at the outer edge. The new lesion was only slightly tender, with a dry base resembling scar tissue.

Histopathology

The skin from the left labium majus was extensively and deeply ulcerated (Fig. 2) The base of

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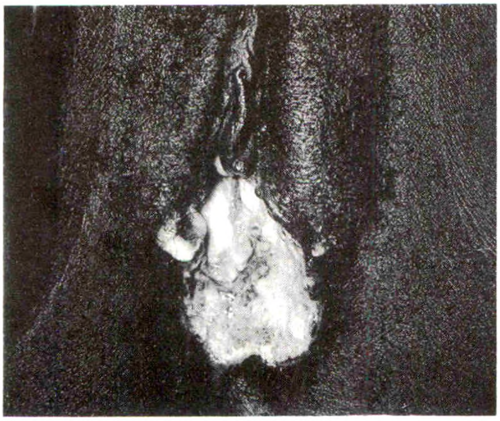

Fig. 1. Photograph of deep acute ulceration in young West Indian woman.

the ulcer was formed by a fibrinopurulent layer over granulation tissue with a chronic inflammatory infiltrate superimposed, in which were numerous collections of neutrophil polymorphs. These seemed to be centred on many blood vessels. Fibrinous necrosis was present in these blood vessels indicating a necrotizing vasculitis (Fig. 3). The vessels involved included small to medium-sized arteries and smaller vessels. The inflammatory and ulcerating process extended into underlying fat. The adjacent intact skin showed only reactive acanthosis, spongiosis and a local moderate, lymphocytic, perivascular infiltrate. No organisms were demonstrated. The features suggested that the vasculitis, rather than infective causes, was aetiologically important and the features were consistent with pyoderma gangrenosum.

In view of the biopsy result, negative serological and microbiological results and rapidly deteriorating condition, prednisolone (Deltacortril), 60 mg daily, was added to the new treatment regimen of co-trimoxazole (Septrin), two tablets twice daily, and metronidazole, 400 mg twice daily, which the patient had been taking for the previous 3 days.

The response was dramatic. The ulcer began to heal within 24–48 h and was completely healed and almost totally repigmented, with the appearance of a healed episiotomy scar, within 4 weeks.

The prednisolone therapy was continued for 5 weeks, then the dose was gradually reduced and eventually stopped 6 weeks later. The co-trimoxazole and metronidazole were discontinued after 3 weeks and 1 week of treatment, respectively.

When last seen 18 months later the patient was still fit and well.

Discussion

Genital ulceration is one of the most difficult diagnostic problems in genitourinary medicine (Piot & Meheus 1985). It may be infective (viral, bacterial or spirochaetal), neoplastic, traumatic or vascular in origin. The cause remains unknown in many patients (Sturm *et al.* 1987).

Our patient illustrates the difficult diagnostic and therapeutic problem of acute genital ulceration. She showed no evidence of infection, sexually transmitted or otherwise, and no suggestion of trauma or self-induced injury. The final dramatic response to treatment was almost certainly due to the prednisolone, and the initial improvement following local triamcinolone adds weight to this theory.

In 1904 Lipschütz (Finnerud 1926) first described a vulval condition he named *Ulcus*

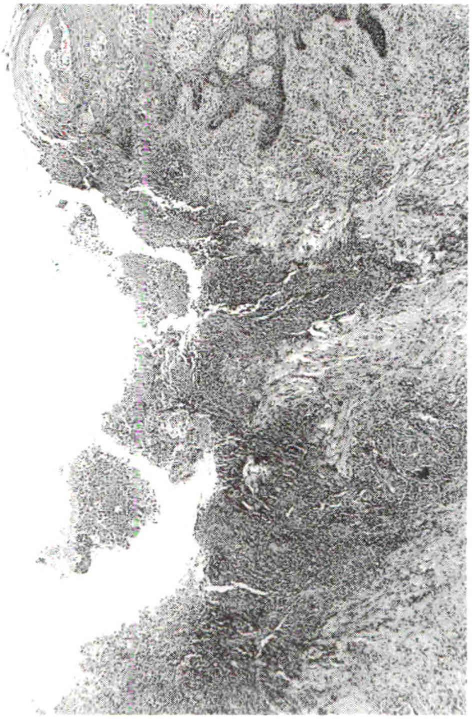

Fig. 2. The margin and depth of one side of the ulcer is illustrated. It has a base of necrotic slough and inflammatory infiltrate. The epidermal margins show only mild reactive changes. ×6.

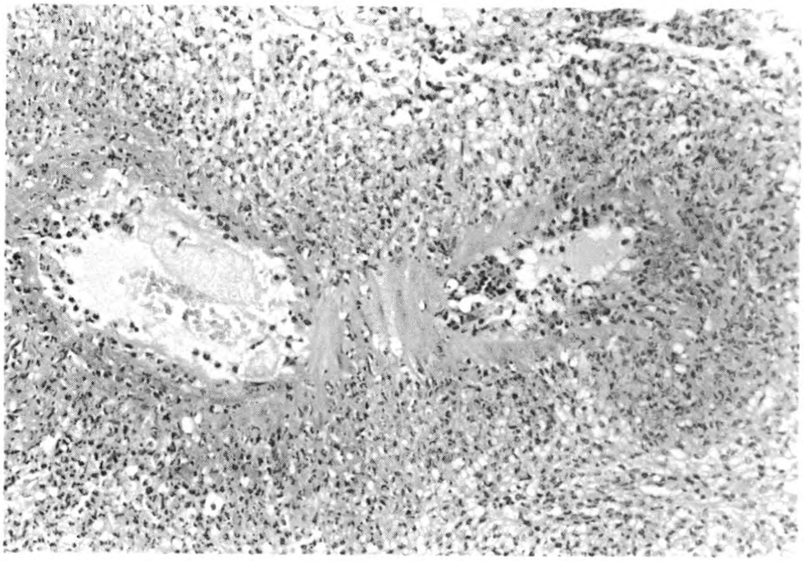

Fig. 3. A vessel in the tissues deep to the ulcer shows florid necrotizing vasculitis. ×25.

vulvae acutum from which he isolated an organism, *Bacillus crassus,* indistinguishable from Doederlein's bacillus. A later review of his work (Finnerud 1926) suggested that there were two different ulcerative patterns.

One variety, a gangrenous form with deep discoid ulcers, healed with scars and was associated with systemic symptoms; the other variety, described as the veneroid form due to the resemblance to chancroid, presented with shallow, exquisitely tender, non-indurated, sharply defined ulcers with serrated edges and an erythematous halo. The base was covered with a fibrinopurulent discharge. They were usually situated on the medial aspect of the labia minora and not associated with systemic symptoms. These lesions presumably healed without scarring.

The clinical findings in our patient are somewhat similar to the description of the second variety of Lipschütz's ulcer. However, he described his lesions before viral or autoimmune disorders were known and some cases, probably those of the first variety, are now thought to be Behçet's disease (King *et al.* 1980).

Behçet's disease is a chronic relapsing ulcerative condition of unknown cause. It is usually associated with oral ulceration in the early stages, but may present with genital ulceration alone. It may also be aggravated by menstruation.

The past history in our patient is suggestive of Behçet's disease, but the extent of the ulceration, lack of other signs and complete response to steroids, are rather against this diagnosis. Time may be the deciding factor.

Necrotizing fasciitis, or synergistic gangrene, is a rapidly progressive and often fatal infection occurring after surgery (Hutchinson *et al.* 1976). Spontaneous involvement of the vulva has been described, but in a series of 22 patients all were diabetic, apart from one (Roberts & Hester 1972; Roberts 1987); in all of these cases the destruction extended well beyond the vulva on to the adjacent thigh or abdominal wall. Neither of the predisposing factors was present in our patient and bacteriology was negative, but she had been treated with an antibiotic for 2 days before the swabs were taken.

Pyoderma gangrenosum, therefore, appears to be the most likely diagnosis in this case. It may present with rapid necrosis of tissue and a single deeply penetrating ulcer; it may also, rarely, be confined to the genitalia (Sanusi *et al.* 1982). No evidence of systemic disease is found in as many as 50% of patients with this condition (Wolff & Stingl 1987).

Pyoderma gangrenosum responds to oral corticosteroid therapy though the response is not usually as rapid as it was in our patient. Clearly long-term follow-up over many years is essential in a case of this kind, if it is possible, where the diagnosis is in doubt.

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SHORT COMMUNICATIONS

Hyperglycaemic hyperosmolar syndrome complicating severe pregnancy-induced hypertension. Case report

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Case report

A 30-year-old woman in her sixth pregnancy was admitted to hospital at 30 weeks gestation because of elevated blood pressure (160/120 mmHg), proteinuria 4+, generalized oedema and hyper-reflexia.

The pregnancy had been uncomplicated except for a mild microcytic hypochromic anaemia. She had had three spontaneous term deliveries, one preterm delivery and one early induced abortion. Her medical history was uneventful. On admission the patient was drowsy, dysarthric but was orientated to person, time and place. She was apyrexial with a pulse rate of 88 and respiratory rate of 18/min. The uterine size was compatible with 26 weeks gestation. Ultrasound examination demonstrated a fetus corresponding to 27 weeks gestation and severe oligohydramnios. The cervix was posterior, closed and uneffaced.

Cardiotocography showed a mild baseline tachycardia with normal short- and long-term variability. No uterine contractions were detected.

On admission, peripheral and central venous lines were inserted. Initial laboratory investigations, including haemoglobin concentration, coagulation tests and platelet count, were normal, except for mild haemoconcentration (Hb 13·2 g/dl). Plasma ions and blood urea nitrogen (BUN) were normal (Na 142 mEq/l, K 4·6 mEq/l, Cl 92 mEq/l, BUN 2·6 mmol/l) while an extremely high blood glucose level of 63·8 mmol/l (1150 mg/dl) was found. The serum glucose level was repeated via a CVP line and found to be 60·2 mmol/l (1084 mg/dl). Plasma osmolarity was 381 mosmol/l, arterial pH was 7·33, Pa,co_2 35 mmHg, Pa,o_2 92 mmHg, HCO_3 20 mmol/l, BE- 5 mmol/l and lactate 0·6 mmol/l. Urine analysis revealed protein 3+, glucose 2+, and no blood or ketone bodies were present.

Blood pressure was successfully controlled by intravenous hydralazine, 200 μg/min. Magnesium sulphate was injected in doses of 4 g intravenously and 10 g intramuscularly. Two hours after admission regular insulin administered intravenously at a rate of 10 iu/h was started. The patient's level of consciousness decreased and 3 h after admission she was comatose. Her blood glucose was 39 mmol/l (685 mg/dl), her blood pressure 150/90 mmHg, and plasma osmolarity 331 mosmol/l. Fluid balance was maintained by the infusion of Ringer lactate solution.

Neurological examination revealed internuclear ophthalmoplegia, vertical nystagmus and a hyporeactive gag reflex consistent with brain stem encephalopathy. Arterial blood gases showed a mild metabolic acidosis with a partial respiratory compensation.

Four hours after admission blood glucose levels had decreased to 16 mmol/l (290 mg/dl) and blood pressure varied between 150/90 and 170/115 mmHg. The patient was still in coma. Urine output varied between 70 and 95 ml/h. No further measurements of osmolarity were made. Under general anaesthesia a lower uterine segment caesarean section was performed. A female infant weighing 930 g with umbilical vein blood pH of 7·25 and Apgar scores of 7 and 9 was born. Except for transitory hyperglycaemia of 10 mmol/l (180 mg/dl) decreasing to normal levels within 24 h, and mild hyperbilirubinaemia, the infant suffered no respiratory or metabolic complications. Examination of the newborn suggested a gestation of 30 weeks and growth

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retardation. The postoperative course was characterized by severe hypertension requiring nitropruside intravenously in doses of 2000–3000 µg/min for 3 days. Regular insulin in doses of 16 iu/day in two equal doses was necessary to control the hyperglycaemia for 3 more days. By the second postoperative day, the patient was fully conscious and co-operative. The neurological findings had improved markedly.

Ten days after admission the patient was neurologically normal and normotensive (130/80 mmHg). She was discharged with no medication. Six weeks later an oral glucose tolerance test was found to be normal.

Discussion

Non-ketotic hyperglycaemic coma is usually associated with febrile illnesses such as Gram-negative sepsis, acute pyelonephritis, bronchopneumonia, and acute viral infections, or precipitated by acute conditions such as myocardial infarction, pulmonary embolism, cerebro-vascular accident or acute pancreatitis (Arieff & Carroll 1972).

The pathophysiology of this condition is not clear. While the maximum rate of glucose production in a fasting subject is less than 100 g/day the brain utilizes more than this amount daily. Hyperglycaemia can only be maintained in the absence of glucose intake if there is reduced glucose metabolism in the brain or by the utilization of non-glucose energy source as free fatty acids or beta-hydroxybutyrate. Since the beta-hydroxybutyrate levels are excessively high in these patients it appears that this source of energy is utilized in this syndrome resulting in excessively raised blood glucose levels. Ketoacidosis is virtually absent despite the very high levels of beta-hydroxybutyrate (Mitchell *et al.* 1985).

To our knowledge this is the first reported case of HHS associated with severe pregnancy-induced hypertension (PIH). Since severe PIH may be complicated by disturbances in consciousness, HHS should also be considered in the differential diagnosis. Excessively high blood glucose levels with absence of urinary ketone bodies makes this diagnosis probable and can be confirmed by normal plasma ketone body anion concentration and hyperosmolarity. Because a hypovolaemic state characterizes this syndrome, 0·5 N (0·45%) saline should be infused, the rate being determined by central venous pressure and urinary output. Our patient did not receive this treatment. In this case, as has been reported by others (Arieff & Carroll 1972), low-dose insulin (10 iu/h) intravenously was effective in reducing the high level of glycaemia so avoiding the possible occurrence of hypoglycaemia and hypokalaemia. Generally minor acid-base imbalances are self correcting.

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A gynaecological complication of polymyalgia rheumatica/giant cell arteritis

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Case report

A 65-year-old woman (para 0+0) presented to her general practitioner with a 3-month history of pain and stiffness in the neck, shoulders, arms and hips. An ESR (Westergren) was elevated at 95 mm in the first hour. A provisional diagnosis of polymyalgia rheumatica was made and an outpatient appointment arranged. Two months later, before her outpatient appointment, she developed severe lower abdominal pain which localized to the left iliac fossa and she was admitted to hospital. On examination, her abdomen was soft with slight tenderness and a mass was palpable in the left iliac region. Ultrasound examination showed a large left ovarian cyst which was confirmed at laparotomy, and a total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy was performed. Postoperatively she made an uneventful recovery.

Subsequently she attended the rheumatology outpatient clinic when the diagnosis of polymyalgia rheumatica was confirmed and she was treated with oral prednisolone. Her ESR fell to 12 mm/h over the next 3 months and has remained at this level for the past year, with no further pain or stiffness of shoulder or neck.

Pathology

The surgical specimen consisted of a uterus distorted by intramural leiomyomata, with an endometrial polyp in the uterine cavity. The right ovary and fallopian tube appeared normal. The left ovary was cystic, 12 × 10 × 10 cm, with fallopian tube stretched over the surface. The cyst had a mottled purple wall and contained serous fluid with several small papillary projections on its inner surface.

Microscopic examination showed atrophic postmenopausal endometrium with a benign endometrial polyp, and leiomyomata. The left ovarian cyst was a papillary serous cystadenoma with extensive, but focal, areas of infarction of its wall.

The medium-sized muscular arteries in the myometrium, parametrium and both ovarian hila showed a giant cell arteritis with fragmentation of the internal elastic lamina and a heavy inflammatory infiltrate predominantly of lymphocytes with occasional neutrophils, and focally a granulomatous giant cell reaction (Fig. 1). The mononuclear infiltrate involved both the media and the adventitia.

Vessels in the left ovarian hilum showed severe arteritis with marked intimal proliferation and oedema causing total occlusion of their lumen. We consider this severe giant cell arteritis to be the cause of the infarction of the left ovarian cyst.

Discussion

Giant cell arteritis classically presents with features of temporal arteritis. It occurs in approximately 1 in 750 of the over-50 age group (Hunder & Michet 1985). It is a systemic condition which may affect any medium or large elastic arteries, and is also often associated with polymyalgia rheumatica (Healey 1988).

Giant cell arteritis of the female genital tract is, however, uncommon with only 11 cases reported in the literature. Six of these were associated with symptoms of polymyalgia rheumatica, which include weight loss, headache, neck and shoulder stiffness and an elevated ESR. These cases were all found incidentally in hysterectomy specimens removed for unrelated disease (Polasky *et al.* 1965; Pirozynski 1976; Hugod & Scheibel 1978; Petrides *et al.* 1979; Schiffman 1979; Evans *et al.* 1980; Gloor *et al.* 1982; Lui *et al.* 1985; Kyle *et al.* 1987). Several of the reports comment that no local gynaecological symptoms have been produced by the giant cell arteritis (Gloor *et al.* 1982; Lui *et al.* 1985; Kyle *et al.* 1987).

Our patient initially presented with symptoms of polymyalgia with an elevated ESR, but 2 months before treatment was started she developed severe lower abdominal pain. A subsequent hysterectomy and bilateral salpingo-oophorectomy revealed an ovarian cyst which histologically showed infarction with a severe giant cell arteritis of the left ovarian arteries with occlusion. The arteritis also involved adnexal and myometrial arteries.

This case is of particular interest as it is the first reported case of giant cell arteritis of the female genital tract causing acute local gynaecological symptoms.

Acknowledgment

We are grateful to Mr C. A. R. Lamont for permission to publish this case.

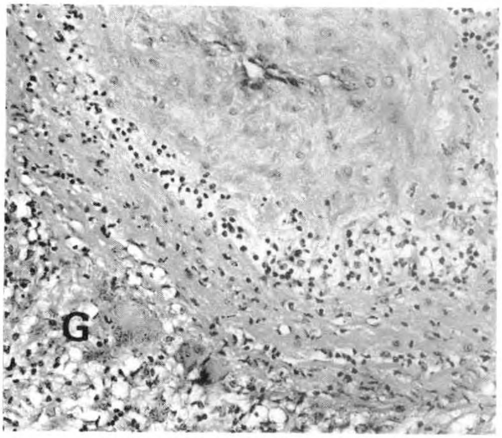

Fig. 1. Ovarian hilar artery showing severe luminal stenosis with giant cell granulomatous (G) inflammation of its wall. Haematoxylin and eosin × 210.

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Erratum

SHORT COMMUNICATIONS

A gynaecological complication of polymyalgia rheumatica/giant cell arteritis

P. J. BIRCH & R. BUCHANAN

Hyperglycaemic hyperosmolar syndrome complicating severe pregnancy-induced hypertension. Case report

A. RAZIEL, P. SCHREYER, P. ZABOW, S. ARIELI & E. CASPI

Unfortunately, these two papers could not be included in the October issue, as indicated in the Contents list, but are now published herewith in the November issue, pp. 1355–1358.

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CORRESPONDENCE

Radiation exposure of the ovaries during hysterosalpingography. Is radionuclide hysterosalpingography justifed?

Dear Sir,
We wish to comment on the article by van der Weiden & van Zijl [*Br J Obstet Gynaecol* (1989) **96**, 471–472] which compares the radiation exposure of the ovaries during conventional hysterosalpingography (HSG) with radionuclide HSG.

They quoted a maximum exposure of 3·74 mGy for HSG with a mean of 1·08 mGy, similar to the reported mean of 1·13 mGy for electronic fluorography (Freedman *et al.* 1987). Higher mean doses for HSG have been reported: 3·66 mGy (Sheikh & Yussman 1976) and 5·25 mGy (Parekh & Arronet 1972) for fluoroscopy and three spot films and 6·75 mGy for three spot films alone (McCalley *et al.* 1985). The National Council on Radiation Protection and Measurements (1977) quoted a much higher figure of 67 mGy not including the dose due to fluoroscopy.

For radionuclide HSG, van der Weiden & van Zijl (1989) quoted the original work of Iturralde & Venter (1981) who gave 370 MBq ^{99m}Tc microspheres resulting in a maximum dose of 281 mGy. However, such doses have never been used in clinical practice. McCalley *et al.* (1985) used 37 mBq with a pinhole collimator but without computerized imaging. They acquired 200 000 counts per image and estimated an administered dose of 0·49 mGy/MBq based on 5% dosage to each ovary and 0·76 mGy/MBq based on a figure of 7·5%.

We used radionuclide HSG to study 32 fallopian tubes in 16 women and compared the results with findings at laparoscopy and hydrotubation performed within 7 days of radionuclide HSG. A sensitive planar collimator with a computer allowed the use of 3–5 MBq. Average counts were achieved of 18 000–20 000 counts per image per 5 min. The highest possible theoretical dose was 0·76 × 5 = 3·8 mGy per ovary although our patients showed a maximum uptake of 4·6% giving a maximum dose of 0·47 × 5 = 2·35 mGy. At laparoscopy, 30 tubes were patent of which only 13 appeared patent with radionuclide HSG. The remaining two tubes were blocked at laparoscopy but patent with radionuclide HSG.

Our finding of 41% (13/32) efficiency for radionuclide HSG (percentage of tubes correctly classified) compares favourably with the value of 49% obtained by Brundin *et al.* (1989) but not with the 94% efficiency reported by McCalley *et al.* (1985). Nevertheless, we feel that radionuclide HSG may represent a more accurate test of tubal function than conventional HSG or hydrotubation and that it is as safe as conventional HSG considering the low radiation doses that can be used with modern collimators and computers.

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Authors' reply

Dear Sir,

Our statement that radionuclide hysterosalpingography (HSG) delivers an approximately 25 times higher dose of ionizing radiation to the ovaries was based on the total absorbed dose of 0·76 mGy/MBq (2·8 rad/mCi) given by McCalley *et al.* (1985). They made use of 37 MBq ^{99m}Tc–labelled human serum albumin microspheres.

Dr Kennedy and colleagues are able to lower this dose to 3–5 MBq employing a sensitive planar collimator with a computer. They calculated a highest possible dose of 3·8 mGy, comparable with the maximum exposure for a conventional HSG measured by us (3·74 mGy).

However, using this technique the efficiency for radionuclide HSG dropped from 94% (McCalley *et al.* 1985) to 41%. Moreover, the claimed gain in physiological information with radionuclide HSG is attended with a loss of anatomical details as given by a conventional HSG.

Therefore, we retain our reservations on the use of radionuclide HSG.

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Reference

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The place of laparoscopy in women with ascites

Dear Sir,

We read with interest the paper by Sheth [*Br J Obstet Gynaecol* (1989) **96**, 105–106] about the place of laparoscopy in women with ascites. We were impressed with the high frequency of tuberculosis in the series (29% of all peritoneoscopies) and envy Dr Sheth's large experience. He does not consider ultrasonography for the investigation of women with ascites, perhaps because of limited availability in his country. This important diagnostic tool provides valuable information and may be the reason why laparoscopy has been little used in Europe and North America. We consider that laparoscopy must be used only to resolve certain specific diagnostic problems in women with ascites. One of these is when gynaecological malignancy is suspected but cytological examination of the ascitic fluid is negative. As Dr Sheth has found, some of these women will have a final histological diagnosis of tuberculosis. In this situation, laparoscopy can avoid an unnecessary laparotomy.

This is illustrated by a recent patient of our own. A previously healthy 37-year-old woman had weight loss, exudative ascites, and a right pleural effusion. A tuberculin test (5 units) was negative. Analysis of the pleural and ascitic fluids showed: protein 64/76 g/1, glucose 5·7/5·2 mmol/1, red blood cells 1350/1120 per ml, and leucocytes 2020/2080 (96/97% lymphocytes). No malignant cells were seen on cytological examination. All smears were negative for acid-fast bacilli. Abdominal ultrasonography was performed. The scan showed multiple nodules on the uterine, hepatic and parietal peritoneum surfaces. There was a left adnexal mass, suggesting a stage IV ovarian carcinoma. A laparoscopy was peformed. This showed multiple white miliary tubercles scattered over the same locations and biopsies contained *Mycobacterium tuberculosis*.

Abdominal ultrasound is very useful in the investigation of women with ascites but in certain situations can fail to provide an accurate diagnosis. In these settings, laparoscopy remains an important diagnostic tool and can avoid an unnecessary laparotomy. Tuberculosis is a treatable cause of ascites in women and must always be borne in mind in countries with a low prevalence of this infection because ultrasonography can suggest a false diagnosis of malignancy.

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Pregnancy following simple repair of the ruptured gravid uterus

Dear Sir,

I agree with O'Connor & Gaughan [*Br J Obstet Gynaecol* (1989) **96**, 942–944] that there is a place for conservative surgery in selected patients with rupture of the gravid uterus. However, only two of the 15 patients they reported had rupture involving the upper uterine segment, so no conclusions can be drawn from the article about the management of patients with this type of rupture.

In pregnancy, after repair of uterine rupture, the risk of repeat rupture varies with the site of the original rupture (Ritchie 1971). Patients should be placed in one of three groups: group 1, where rupture was confined to the lower segment; group 2, where rupture involved a classical caesarean section (CS) scar; and group 3, where rupture involved the upper segment but not the classical CS scar.

The risk of repeated rupture is least in patients in group 1. The authors report 16 pregnancies in 13 patients in this group without repeat rupture. This is fresh evidence that successful pregnancy can be achieved in these women if they are delivered by elective lower segment CS at 38 weeks as advised by Aguero & Kizer (1968).

The authors report only one patient in group 2. She was delivered safely at 35 weeks. No new conclusions can be drawn about the management of this group of patients. In a collected series of 13 patients categorized as group 2, some of whom had vaginal deliveries and more than one pregnancy after repaired rupture, there were 6 (46%) who had repeat rupture and one patient died (Ritchie 1971). Delivery by elective lower segment CS at not later than 36 weeks (Sheth 1968) may reduce the risk to these patients. I think sterilization should be seriously considered for the patient in this group who has one successful delivery after repair of rupture.

My main criticism of this article is that the risk to patients in group 3 is not emphasized. Only one patient in group 3 was included. She had a repaired small fundal rupture and she was managed safely as a group 1 patient. In the collected series reported by Ritchie (1971) there were 15 patients in group 3, three (20%) had repeat rupture and no patient died. We do not know how great is the risk for this group of patients. The upper uterine scar is likely to be weaker than the lower uterine scar, especially if posterior, lateral or weakened by infection. These patients call for the same caution in management as we give patients in group 2.

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BOOK REVIEWS

Birthrights. Law and Ethics at the Beginnings of Life edited by Robert Lee & Derek Morgan. Routledge, London, 1989, 222 pages with figures and tables, £30.00

This collection of essays by nine academics, all but two of whom are lawyers, discusses and, in many instances, challenges, the ethical basis for much of the legal regulation of matters surrounding birth, the new technology of birth, surrogacy, embryo experiments, abortion, the management of newborn severely handicapped babies, sterilization, and allied subjects

In view of possibly impending Warnock legislation, it is a timely volume, which should be read by lawyers and parliamentarians who deal with such issues, and by doctors who take an interest in these aspects of medicine. Some of the contributions, however, require a considerable knowledge of the law, and readers lacking this are not given a great deal of assistance in understanding some of the arguments. This is not true of philosopher John Harris's brilliant and provocative contribution 'Should we experiment on embryos?' which might with advantage be made compulsory reading for all taking part in the forthcoming debates.

The strength of this volume is the perception of virtually all the authors that the issues under discussion do not lend themselves to the simple and childish judgements favoured by the extremist pressure groups that operate in this field. 'To suggest', writes Harris, 'that embryo research is in principle permissible, is not of course to say that anything at all may be done to or with embryos. We must always, and always carefully, examine any research protocol to see whether it is justified given what is proposed, what might thereby be achieved, the probability of its success and the cost of undertaking the work; including of course the moral costs and benefits'.

The ethical issues thrown up in this field, by the work of the health economists in particular, are novel and thought provoking. How far, for instance, ought we to go in helping the infertile, in a society that manifestly does not adequately look after the children it already has, in a world in which overpopulation is one cause of mass starvation in several parts of the globe and is producing a catastrophic impact on the natural environment. At a parochial level, as Frances Price notes in her chapter on the management of infertility, community provision for higher order multiple-birth children in both the health and social services is becoming a matter of increasing concern at a time when these services are attempting to cope, very inadequately, with the implementation of welfare policies transferring care into the so-called 'community'. One of the most alarming statistics in this volume is that 'the rate of death by homicide of children under 12 months is nearly three times that of the population as a whole' Using available resources to save some of these children might be thought to have a higher priority than helping to produce many more.

Problems of resource allocation are also relevant to the issue of how far we go in resuscitating extremely low birthweight infants who could not have been resuscitated a decade ago, and who will require care for the rest of their lives, often by those (usually parents) who had no say in the decision to save this life. Celia Wells, in her interesting essay on 'Marginal children' points out that it is necessary to start by trying to decide whether even if resources were plentiful, it would be justified to refrain from treating some babies. If so, then resource issues and questions of priority only enter in at the next stage of the argument in relation to those infants who in principle are deemed worth saving because of the likely quality of their future lives. She notes that the most forceful opposition to non-treatment tends to come from those who have least contact with neonatal units. She might have added, and from those who are not themselves prepared to volunteer for a lifetime's caring. The moral issues involved in making decisions that will result in appalling hardship not for oneself, but for other people, is a central ethical question in this field that still remains to be fully explored.

Madeleine Simms

Critical Care Obstetrics edited by S. L. Clark, J. P. Phelan & D. B. Cotton. Medical Economics Books, Oradell, NJ, 528 pages with figures and tables, $52.95

This would be a very useful book to have on the labour ward shelf. Catastrophes occurring in obstetrics, such as amniotic fluid embolus, fulminating pre-eclampsia, diabetic ketoacidosis and even thyroid storm, are considered systematically with a one-page resumé of management following each section. The topics are heavily biased towards cardiovascular and respiratory complications so it is not surprising that there is considerable reliance on the Swann–Ganz catheter for measurement of cardiac outputand left-sided filling pressures. If this is to be used in the UK it will usually entail transfer to a separate non-obstetric intensive therapy unit; and the clinicians will need to balance carefully the advantages and the disadvantages of such a move. Surprisingly, I could find no mention of the management of seizures in the patient with severe hypertension. Perhaps it is so accepted that magnesium sulphate rules in the USA that no further comment is necessary!

Despite this criticism I would recommend the book to all who care for severely ill pregnant women.

M. de Swiet

Perinatal Events and Brain Damage in Surviving Children edited by F. Kubli, N. Patel, W. Schmidt & O. Linderkamp. Springer-Verlag, Berlin, Heidelberg, New York, 1988, 338 pages with figures and tables, DM 120

Professor Kubli, Chairman of FIGO, organized a workshop in Heidelberg shortly before his death, and this volume is dedicated to him and reports the proceedings. The large number of contributions (62) and papers (37) presented inevitably means some overlap and unevenness, but the final result is very readable, and the volume works as a 'state of the art' review of the aetiology of cerebral injury in the newborn.

The first section on epidemiology begins with crisp reviews on definitions and the scale of the problem, with a distinctive Swedish slant. Mechanisms are then covered from genetic, developmental, traumatic and asphyxial standpoints. The latter chapter presents yet another analysis of the ageing collaborative perinatal study, but the conclusions that acute hypoxia rarely plays a role in long-term neurological abnormality will cheer many an obstetrician. Growth retardation as a precursor of brain damage is then tackled with reviews on recognition and cause, but the section becomes rather confused where management is considered, with one author reviewing the lack of evidence for the efficacy of bed rest and then recommending it in the following paragraph.

The chapters dealing with asphyxia make valuable reading for any perinatologist, with Dr Adrian Grant's review on the relation between obstetrically preventable asphyxia and outcome quite the best argued in the book. I notice that it has been cited already in two recent papers on the subject!

Intracranial haemorrhage and ischaemia are covered in six concise chapters, but do not contain particularly new material, although very readable. The remainder of the book consists of papers on prognosis and follow-up; these tend to be rather parochial in nature and, although one or two are geographically based, most are hospital studies.

Overall, there is plenty in this slim well-referenced volume for the obstetrician interested in the long-term outcome of high-risk babies.

R. W. I. Cooke

Atlas of Fetal Skeletal Radiology edited by Asher Ornoy, Zvi Borochowitz, Ralph Lachman & David L. Rimoin. Year Book Medical Publishers, Inc., Chicago, London, 1988, 147 pages with figures and tables, £61.00

There is a paucity of publications on fetal radiography, and the concept behind this atlas is excellent. There is a real need to encourage the radiography of miscarried and stillborn fetuses and for a standard reference on the normal appearances. In many ways this book initiates this process, but I felt it could and should have gone rather further.

There is an excellent first chapter covering the histology of bone development though unfortunately all the histological illustrations are in black and white. Chapter 2 illustrates the normal appearances of the fetal skeleton from 10 to 27 weeks gestation, and all the illustrations are produced at standard magnifications to permit measurement by the reader. Each illustration is accompanied by a standard format text which describes the significant radiological changes detected at each gestational age. Regrettably the radiographic technique, which is very important and very different from standard radiography, is given cursory mention and was clearly not standardized in the production of the material for this atlas. It is essential to use unusually low KV X-rays, to employ fine-grain film, often a magnification technique is helpful, and standard fetal positions should be achieved and radiographs always obtained either before dissection or after a standard eventration and reconstruction of the thorax. Failure to observe these criteria and rather variable photographic reproduction have led to a significant diagnostic loss in many of the reproductions used to illustrate this atlas. The third and final chapter illustrates 19 examples of fetal skeletal dysplasia. The range of variability within each syndrome can often be very large and therefore the individual fetuses used to illustrate some of the diagnoses in this atlas are not entirely typical; indeed one or two are quite atypical. Unfortunately the authors have chosen to dwell in the text on the radiographic findings of the illustrated cases rather than those normally associated with the particular condition.

The book concludes with a comprehensive appendix listing the major skeletal dysplasias by name but this does not include the specific features of each.

I have no doubt that this book will prove very useful to those requiring a standard reference text and can recommend it to anyone with a particular interest in fetal skeletal dysplasias. There is, however, great scope for improvement in both the quality and quantity of illustrative material and text.

Hylton B. Meire

The Developing Human by Keith L. Moore. W. B. Saunders & Co., Eastbourne, 1988, 462 pages with figures and tables, £18.95

This is a good update of a well-known book on embryology. The first edition came out in 1973 and there have been three subsequent editions. Professor Moore does well by using good illustrators who take his points and show them clearly. There are clear, almost three-dimensional drawings; Mrs Angela Cluer and Mrs Marlene Herbst have carefully followed the original work of Glen Reid in modernizing the illustrations.

This is a greatly revised book, and at the very low price of £18.95, it is thoroughly recommended to undergraduates and to those taking high degrees in obstetrics for it is clear and full of clinical application. All postgraduate libraries would do well to have a copy.

Geoffrey Chamberlain

Diabetes Complicating Pregnancy. The Joslin Clinic Method edited by John W. Hare. Alan R. Liss, Inc., New York, 1989, 206 pages with figures and tables, $49.50

This book is from Boston, Massachusetts, more precisely from the team who look after the pregnant diabetic women at the Joslin Clinic in the wake of Luke Gillespie and Priscilla White. John Hare is the editor and chief contributor with four chapters, Vanessa Barss provides two on obstetric management and complications, Michael Greene one on congenital malformations separate from the practical thrust of the book, and one is from John Cloherty and Michael Epstein on neonatal management.

There are three other chapters, from a diabetes nurse educator, a nutrition educator and a medical social worker respectively. A reviewer would have to change gear to embrace these contributions with a similar degree of circumspection to those written by the medical staff at the Joslin Clinic. Two quotes from these narratives might serve to illustrate: 'the importance of education with a chronic disease such as diabetes cannot be underestimated' and 'while it is impossible to set a fixed price for a high-risk pregnancy, general agreement sets the cost in tens of thousands of dollars . . . . ' Suffice it to say that these three accounts indicate the perceived *modus vivendi* of diabetic women in the Boston area and the *modus operandi* of the health care professionals in their chosen roles.

The book is well produced, firmly bound between hard covers. The bibliography is variable and selective. The index is comprehensive. Few books have so few misprints or mis-spellings.

It is easy to be charitable about this chatty little book ('the first issue is how far along in pregnancy the mother is'). Writing a treatise on a subject sometimes helps to clarify thoughts and determine strategies for problem-solving and, at other times, is the emotionally charged spillage from the brimful reservoirs of the mind emerging in the form of a labour of love. This book comes across as a mixture of both. The dedication of the writers to their subject is almost palpable but the scientific basis for some of their protocols fragile. It is strongly opinionated, e.g. 'human insulin is likely to become universal by the end of the century'. The argument for encouraging the puerperal blood sugar to rise to a range of 10–17 mmol/l is unconvincing. The fact that this is a time when abdominal and perineal wounds are in the process of healing is ignored.

John Hare's medical chapters include some clear but obvious statements, e.g. 'The cornerstone of management of diabetes in pregnancy at the Joslin Clinic has been a team approach' and 'The single most important advance in the management of diabetes in pregnancy in the last decade has been the availability of home blood glucose monitoring . . .'. One might have hoped they would also contain detailed evaluation and rationalization of the White classification and management protocols at the Joslin Clinic with equal clarity but reading and rereading was unhelpful. Not all the rereading was determined by the reviewer, e.g. Table I on page 16 and Table I on page 37 are identical—both White classification (revised) in successive chapters by John Hare.

The contents of the medical, obstetric and neonatal chapters cannot, however, be faulted as they describe what happens at the Joslin Clinic. The burden of my criticism is that what happens at the Joslin Clinic can be faulted. This is the principal shortcoming of this text as a useful acquisition to one's library. There appears to be no formal combined diabetes–obstetric prepregnancy clinic which directs metabolic control and contraception until optimal conditions for conception prevail. From this arises their debate about arbitrary termination of pregnancy on the basis of a high glycosylated haemoglobin value or the alternative approach of awaiting a detailed ultrasound scan result at 18 weeks gestation (imagine the anxiety and consequent effect which that may have on metabolic control during the early months of pregnancy). Delivery is planned for 38 weeks because 'there is no fetal benefit to remaining *in utero* beyond this time'. The description of the protocol (page 49) for failed induction with oxytocin on two successive days leading to consequent caesarean section is worrying in these days of allowing women with Type I diabetes, in the absence of complications, to continue to their expected date of delivery, as are the practices of cervical assessment and therapeutic ripening with prostaglandins. Dr Barss suggests that their use for this purpose may be an approach in the future. It therefore comes with less astonishment than otherwise merited to read her statement that 'successful vaginal delivery in our insulin-requiring population is 28%. In Europe we would feel open to criticism with a caesarean section rate of 28%, mindful of the late Dr Ivor Drury's reports from Dublin.

Hand on heart, this book can be recommended only to the *aficionado*. The Joslin clinic method while interesting to read about is not to be followed if one wishes to keep abreast of contemporary practice.

Hamish W. Sutherland

Controversies in Diabetes and Pregnancy (Vol.2 in the series Endocrinology and Metabolism, Progress and Research in Clinical Practice) edited by Lois Jovanovic. Springer-Verlag, Berlin, 1988, 260 pages with figures and tables, DM 128.00

There are no run-of-the-mill offerings in this well-produced and indexed hardback. In her preface Lois Jovanovic challenges the readership to enjoy and profit from this book and appreciate the fervour, assertion and 'sometimes pure faith' permeating the narratives. For me the experience was accurately forecast and she deserves praise for bringing together in an international collection, controversial topics in an attractive mosaic of thought-provoking, scientific essays reflecting contemporary understanding and challenging areas of ignorance. It is a delight to have in one slim volume descriptions of the Cape Town experience with oral hypoglycaemic agents, the Dublin experience on clinical management, the Uppsala view on teratogenesis, and the Phoenix experience of the outlook for the offspring of diabetic Pima Indians. Other topics covered in the book are maternal exercise in gestational diabetes, fetal surveillance, metabolic sequelae in the infant of the diabetic mother, adaptation of the fetal pancreas to maternal diabetes, retinopathy, thyroid disorders in pregnant women with Type I diabetes, and the use of human fetal pancreatic tissue for transplantation. There is also a remarkable short chapter on the adaptation of the fetal pancreas to maternal diabetes by Foa of less than four pages excluding the six pages of references, which is courageously apt.

Sadly I suspect that the chapter from the late Ivor Drury (Fellow *ad eundem*) must have been one of his last to medical literature. Born of long experience and dedication, and given with his characteristic amalgam of conviction and caution, his conclusions are that in uncomplicated well-controlled cases of Type I diabetes, spontaneous labour at term may be awaited; that it is possible to avoid prolonged expensive hospitalization; and that intensive expensive programmes of fetal monitoring are in most cases unnecessary. For this and other gems the book tempts this reviewer tooffer a money-back guarantee if the reader's interest is not stimulated. Alas, at present exchange rates 128 DM is a substantial, albeit singular, disincentive.

Hamish W. Sutherland

Books received some of which will be reviewed at a later date

Drugs and Human Lactation edited by P. N. Bennett. Published on behalf of the World Health Organization by Elsevier Science Publishers, Amsterdam, 1988, 589 pages with figures and tables, US $223.75 or Dfl 425 00

The Baby Under 1000 g edited by David Harvey, Richard W. I. Cooke & Gillian A. Levitt. Wright, London, 1989, 353 pages with figures and tables, £65.00

Diabetes and Pregnancy by P. Chahal & D. F. Hawkins. Butterworths, London, 1989, 168 pages with figures and tables, £25.00

No Fault Compensation in Medicine edited by Ronald D. Martin & John Harvard. Royal Society of Medicine Services Ltd, London, 1989, 290 pages, available through booksellers or Hoddle Doyle Meadows Ltd, Old Mead Road, Elsenham, Bishop's Stortford, Herts CM22 6JN, £20.00

ABC of Clinical Genetics by Helen Kingston. British Medical Association Publication, London, 62 pages, UK £10.95, abroad £13.00 including postage by air abroad

Handbook of Contraception and Abortion by Ronald T. Burkman. Little, Brown & Company, Boston, Toronto, London, 150 pages with 30 illustrations, £13.95

Emergency Transport of the Perinatal Patient edited by Mhairi G. MacDonald & Marilea K. Miller. Little, Brown & Company, Boston, Toronto, 1989, 244 pages illustrated, £26.50

Getting Pregnant: The Woman's Answer Book by Robert Winston. Anaya Publishers, London, 1989, 253 pages with figures and tables, £8.95

Proceedings and Symposia

Sperm Measures and Reproductive Success. Institute for Health Policy Analysis Forum and Science, Health and Environmental Risk Assessment *(Progress in Clinical and Biological Research*, Volume 302). Proceedings of the Workshop, Sperm Measures and Reproductive Success, held at the Aspen Institute at Wye Plantation, Queensland, Maryland, 1988, edited by Edward J. Burger Jr, Anthony R. Scialli, Alexandra N. Bernstein, Robert G. Tardiff & Harold Zenick. Alan R. Liss, Inc., New York, 1989, 313 pages with figures and tables, $64.00

British Journal of Obstetrics and Gynaecology
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COMMENTARIES

Domestic violence: one outlook

The article in this issue of the journal (p. 1379) on the 'Gynaecological impact of sexual and physical abuse by spouse' in Norway is discouraging. Discouraging because it finds, in Norway, the same kind of widespread physical and sexual abuse of women that we find in the USA. It is a confirmation of behaviour that we would rather not see. The study also reports a relation between such abuse and sexual and gynaecological complaints and problems.

In the USA, the Surgeon General became concerned about domestic violence some years ago and convened a 'Surgeon General's Workshop on Violence and Public Health'. Two recommendations emerged from that workshop. The Surgeon General was 'urged to do whatever he could to inform the American people of the epidemic of violence that infects over a million homes every year'. In addition, a second more specific recommendation urged 'the medical profession, and obstetricians and gynaecologists in particular, to do whatever they could do to stop the violence against women, pregnant women, and infants'.

The Surgeon General, C. Everett Koop, asked The American College of Obstetricians and Gynecologists to take up this challenge, and we did. We developed a set of guidelines prepared by Morton A. Stenchever, MD, and Diane H. Stenchever, MSW, in a Technical Bulletin (ACOG 1989) for our 28 000 Fellows along with patient education materials so that each obstetrician-gynaecologist would, at least, have the minimum tools with which to deal with this population at risk.

In the USA, more and more attention is being paid to the plight of women who are the victims of domestic violence. Law enforcement officials, support groups, safe houses, and local coalitions to combat domestic violence are becoming more and more visible. Approximately 1200 shelters and state and local coalitions, although still not adequate to handle the problem, are available. Along with the greater interest on the part of the law enforcement officials and the courts, we now hope and expect that greater numbers of physicians will pay more attention to the problem.

The information we sent to the obstetricians and gynaecologists in the USA will raise awareness and help them detect when one of their patients is the victim of battering. It also helped our physicians explain women's legal rights, gave them information about social services, agencies, organizations and safe houses that are available to women, and an explanation of strategies for helping women escape from situations in which they or their children will be battered.

In addition, we provided patient information that the physician can use to tell women how to escape or change an abusive relationship. We provided our physicians with the information they could use to help their patients.

Family violence and abuse is often a well-kept secret in the USA. Because obstetricians and gynaecologists are the health professionals who care for many women, they play a vital role in detecting when a woman may be the victim of abuse. In addition to sexual and physical abuse, intimidation and psychological abuse occur. Abused women often do not report abuse because of embarrassment and humiliation, many fear pursuit and retaliation, severe injury to themselves or their children or even death. Some women, especially full-time homemakers and mothers, have no other financial support or housing except from the abusive spouse. Abandoning their home, especially with young children, to hide in a public shelter or be homeless is a frightening alternative.

The ACOG *Technical Bulletin on the Battered Woman* contains guidance for obstetricians and gynaecologists for their patients. If an abusive partner refuses counselling and will not change his behaviour, women should be encouraged to report the abuse, tell a trusted friend or family member, identify resources within their community and establish a plan for escape and exit. The woman should be encouraged to plan ahead so that she is prepared to leave with money in cash, a cheque book, credit cards, car keys, driver's licence, clothing, toilet articles and other necessities and toys for children. She should also have financial and legal documents such as birth certificate, social security card, mortgage and utility bills so that she is prepared to establish residence and eligibility for programmes and assistance if necessary. She should know police, ambulance and emergency telephone numbers and the site of a safe house or shelter in case of emergency in the absence of family members who can be relied on to assist her.

There has long been a lack of treatment programmes for abusers in the USA; they are predominantly male. As ACOG's information points out, the abuser often refuses to take responsibility for the abuse and blames the woman victim for causing the violent acts. He often expresses contempt for women, cannot tolerate autonomy in a female partner and views the woman as a possession. He has rigid expectations of marriage and sexual behaviour and believes that she should care for him and the household like his mother did.

His behaviour patterns may be aggressive and assertive and he may have used violence as a way to handle problems. However, abusers may be charming and manipulative, and it may be difficult to believe they exert a violent and abusive relationship with their wife and children.

We know that the batterer often comes with the woman to the emergency room or medical appointments and tries to stay close at hand during the examination so that he can monitor what is being said. The physician should be suspicious if the woman is hesitant to provide information about how she was injured, especially if her explanation does not fit the injuries that are observed. The doctor's ability to recognize the abused woman will often depend on his or her index of suspicion.

Doctors should pay particular attention during an examination to women who have injuries on their head, neck, chest, abdomen, breast or arms. A woman who tries to defend herself often suffers severe injuries including fractures to her upper extremities.

It is so important to identify these women because they are marked for further physical injury if nothing is done to break the cycle of abuse. They are at high risk for suicide or homicide, and their children are in equal danger.

There is evidence that childhood sexual abuse may have occurred in as many as 25% of American women (Bachmann *et al.* 1988). Also families in which spousal abuse occurs may be families in which child abuse is present. Sexual abuse often occurs within a background of physical violence. Unfortunately, children who have been sexually or physically abused may become abusers in the families which they subsequently establish. A woman who is or has been abused may abuse her children. Thus it is essential to identify and repair this cycle of family abuse and violence.

The guidelines we sent to the Fellows of our College advise them how to recognize the woman who might be the victim of abuse. These women visit clinics, emergency rooms or doctors frequently. Some make appointments and do not keep them. If they are not being treated for severe trauma, their complaints include headaches, insomnia, choking sensations, and stomach, chest, pelvic and back pains. When they come into the office or clinic, they appear shy, frightened, embarrassed, evasive, anxious, or passive. And they may often cry.

Battered women have low self-esteem and low self-confidence. They feel helpless, fearful and shameful. They may have conflicting feelings of love and loyalty towards the batterer. Often, they may be prevented by control and fear from planning or acting on their own behalf. Battered women often believe they can control the abuser by trying to please him or avoiding making him angry.

These women may be from any segment of society. Woman battering is not confined to low socio-economic groups. It's not something that only happens to poor women. It happens in any racial and economic group. And it is time that it stopped.

Newspapers, radio and television stations in all parts of our country responded quickly to ACOG's announcement of its programme. The favourable media attention was mirrored by the flood of telephone calls and letters that the ACOG received from law enforcement officials, domestic violence councils, and interested citizens who wanted more information, wished to express their pleasure at having us as allies in this effort, and even from people who wanted personal help. We had certainly touched a raw nerve. However, Nancy Foley writing in the *Providence Journal* complained about ACOG's effort, stating that 'once again, an effort to end domestic violence focuses almost entirely on the victims . . . Domestic violence will not end until society realizes the solution does not lie in forcing the victim to flee her home and hide in a shelter, but in removing the abuser from the house and locking him up in prison'.

The article by Schei and Bakketeig in this journal makes the important point that women who reported sexual or physical abuse had significantly more sexual problems and gynaecological complaints and problems. While ACOG's programme stresses the importance of physical and sexual abuse it has not emphasized to date the associated gynaecological and sexual problems for which these women will require assistance. These problems were not unique or different from the sexual and gynaecological problems often reported at obstetric and gynaecological visits, signifying that questions about sexual or physical abuse should be a routine part of an obstetric and gynaecological history and that uncovering and identifying these problems may be the first step in initiating appropriate counselling and care.

The attention which a national medical association can bring to a problem like family violence, and in so doing enlist its members in assisting their patients, may play an important role in improving women's lives and those of their families.

As Dr Koop said (I think it bears repeating) 'We say we are a civilized society. All right, let's act like one, and let's stop the violence in our families. Let's end the battering of the women'.

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Is ultrasound of any value in screening for Down's syndrome?

Down's syndrome is not a notifiable disorder, and so the exact number of affected babies born each year is not known, although the prevalence is approximately 1.3/1000 births. Although the cost of caring for an affected child can be estimated, the emotional toll and family disruption that follows the birth of such an infant cannot be quantified.

At present, maternal age is the primary indication for cytogenetic diagnosis by amniocentesis or placental biopsy. Maternal age above which diagnosis is offered varies between 35 and 38 years. This cut-off identifies a high-risk population that constitutes about 5% of livebirths. The Down's syndrome babies born to this high-risk group are about 30% of all Down's syndrome babies; the remaining 70% are born to the younger unscreened mothers. For numerous different and complex reasons (Ferguson-Smith 1983) only 50% of this high-risk group undergo prenatal diagnosis so that fewer than 15% of affected pregnancies are detected (Wald & Cuckle 1987). Maternal age is an inefficient screening test for pregnancies affected by Down's syndrome.

Merkatz *et al.* (1984) described an association between low maternal serum alpha-fetoprotein (MSAFP) and fetal chromosomal abnormalities, and in particular Down's syndrome. When maternal age is used in conjunction with MSAFP below specified maternal-age-dependent cut-off levels, 40% of Down's syndrome pregnancies would be detected and 6·8% of unaffected pregnancies—a considerable improvement on maternal age alone (Cuckle *et al.* 1984).

Other tests have been added to this. Maternal plasma unconjugated oestriol, mainly of fetal origin during pregnancy, is reduced in pregnancies affected by Down's syndrome, possibly as a result of reduced or delayed production in the fetal liver. When used in combination with maternal age and MSAFP the detection rate of Down's syndrome at a risk cut-off level of 1:250 improves to 45% with a false-positive rate of 5·2% (Wald *et al.* 1988*b*).

Human chorionic gonadotrophin (hCG) levels are increased in maternal plasma in affected pregnancies. Using all the above criteria together, about 60% of Down's syndrome babies would be detected. The rate of amniocentesis in the advanced-maternal-age group would be reduced as serum screening could place an older woman in a low-risk category, thus increasing the cost-effectiveness of serum screening (Wald *et al.* 1988*a*).

Can ultrasound do as well?

It is with these statistics that ultrasound must be compared. Biochemical tests are dependent on standard assay techniques, while ultrasound requires considerable expertise and there are major differences in quality control, skill and equipment between departments. However, on the recommendation of the Royal College of Obstetricians and Gynaecologists, nearly all pregnant women are scanned between 16 and 20 weeks (RCOG 1984). Ultrasound screening should therefore not require much additional expenditure.

What would ultrasound look for?

A number of morphological features distinguish fetuses with Down's syndrome from normal fetuses. Down's syndrome infants and children are brachycephalic. This obvious clinical sign can be expressed as the cephalic index (biparietal diameter: occipitofrontal diameter). Perry *et al.* (1984), in a study of 316 mid-trimester pregnancies, eight of which were affected by Down's syndrome, showed convincingly that the cephalic index was of no value in screening.

Eight other features have been combined into a diagnostic index for the early diagnosis of Down's syndrome in the newborn (Rex & Preus 1982). The only one of any potential for ultrasound screening was the increase in the nuchal skin thickness. This has been studied in 1704 high-risk pregnancies in two separate series (Benacerraf *et al.* 1985*a*, 1985*b*); one was retrospective and the other prospective. A total of 11 pregnancies was affected by Down's syndrome, a rate of 1/155, and four of the 11 affected pregnancies had shown an increase in nuchal skin thickness and there was one false positive, a sensitivity of 36% and a specificity of 99·9%.

However, a number of criticisms can be made. Flexion and extension of the fetal head can alter nuchal skin thickness. The sign can be produced artificially by angling the ultrasound transducer across the fetal head through a plane that includes the cavum septum pellucidum and the cerebellum. Chromosomally normal fetuses may have an increase in the nuchal skin although the frequency of this is not known (Toi *et al.* 1987). Furthermore, the rate of Down's syndrome in these two studies was high. The positive predictive value of an increase in the nuchal skin thickness was 80% which is extraordinarily accurate when compared to the use of maternal age for screening, but when the data are applied to a normal low-risk population (maternal age <30), the positive predictive value falls to 20% with a false-positive rate of 80% (Toi *et al.* 1987). An increase in nuchal skin thickness is more likely to detect a normal mid-trimester fetus, and the use of this ultrasound sign alone is of little value in screening for Down's syndrome.

The Boston and Newhaven groups published further data associating short fetal femur length with Down's syndrome. In a retrospective study Lockwood *et al.* (1987) found that femur lengths were significantly shorter and the biparietal diameter: femur length (BPD:FL) ratio was consistently elevated in fetuses with trisomy 21. The detection rate was between 50 and 70%. In a second retrospective study on femur length (Benacerraf *et al.* 1987) which was an extension of the first, they looked at a linear regression ratio to assess the relation between the biparietal diameter and femur length, together with an actual-to-expected femur length ratio. Furthermore, they added other ultrasound features such as increased nuchal skin thickness, cystic hygroma and atrioventricular septal defects to an abnormal ratio to improve the sensitivity and specificity of these signs. Some centres would regard the detection of these other abnormal morphological features a sufficient indication for fetal chromosome analysis.

Once more the major criticism of this work is the use of a high-risk population, presumably the same as in the other reports from this group. The excellent identification rate of affected pregnancies from this study masks this very important point. Moreover, using standard tables for biparietal diameter, femur length and gestational age, which are not subject to mathematical formulae, Winston & Horger (1988) investigated 10 fetuses with Down's syndrome. They were unable to confirm the reported association between Down's syndrome and short femur lengths in the second trimester.

More recently, Lynch *et al.* (1989) reported a study of twin pregnancies discordant for Down's syndrome. They found that neither the BPD:FL ratio nor the actual: expected FL ratio was useful in distinguishing the abnormal from the normal fetus although an increase in the nuchal skin thickness was found in 56% of the fetuses with trisomy 21 and in none of the normal co-twins.

The study published in this Journal by Cuckle *et al.* (p. 1373) on femur length presents data from a large retrospective multicentre study in the UK. They derive expected femur lengths from linear regressions of femur length on BPD as did Benacerraf *et al.* but the improvement in the detection rate from 30 to 34% is less impressive than that reported by the Boston Group (50–70%).

Thus, the published data on ultrasound are conflicting and no single morphological feature appears to be useful. The ingenuity of the Boston sonographers has not yet been exhausted. Even hypoplasia of the middle phalanx of the fifth digit has been considered (Benacerraf *et al.* 1988). This also would appear to be an impractical physical marker for screening.

So what is the best combination? Ultrasound, biochemistry or both?

Biochemical screening seems to perform better, but there are no prospective studies to compare the two either separately or in combination.

There is pressure to move away from late to earlier chromosome analysis either by chorion villus sampling or early amniocentesis (Canadian Collaborative CVS–Amniocentesis Clinical Trial Group 1989; Rooney *et al.* 1989). In the future, more work on screening for Down's syndrome will focus on the first trimester; some reports have suggested that MSAFP levels in affected first-trimester pregnancies are lower than in unaffected pregnancies (Brambati *et al.* 1986; Barkai *et al.* 1987; Cuckle *et al.* 1988; Mantingh *et al.* 1989).

Another novel approach being investigated currently by the St Bartholomew's Hospital group is first-trimester sonography to measure yolk sac diameter, for which vaginal probes would be well suited (H. Cuckle & N. Wald, personal communication). The basis for this is that the yolk sac produces AFP, and the low MSAFP levels in affected first-trimester pregnancies could be due to a small yolk sac. However, Reece *et al.* (1988) were unable to distinguish between the yolk sacs of karyotypically normal and abnormal trisomic fetuses.

The importance of this subject is stimulating a great deal of interesting work, but for the present the place of ultrasound is in dating pregnancies, guiding sampling procedures and in detecting the malformations that may be associated with trisomies.

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Ultrasound fetal femur length measurement in the screening for Down's syndrome

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Summary. The fetal femur length determined by an ultrasound examination at between 13 and 39 weeks gestation in 83 pregnancies associated with Down's syndrome was statistically significantly less than the expected value for pregnancies with the same biparietal diameter examined in the same ultrasound department ($P<0\cdot0001$). Expected values were based on linear regressions of femur length on biparietal diameter in 1340 control pregnancies from 27 ultrasound departments. The median value for the affected pregnancies was 0·94 times the expected value (95% CI 0·92 to 0·97). Eleven per cent of affected and 1·4% of control pregnancies had values $\leq 0\cdot85$ times the expected. The reduction in femur length in affected pregnancies was not related to biparietal diameter or to maternal age. Fetal femur length may be useful as an ancillary screening variable in the antenatal screening for Down's syndrome.

The results of two studies showed that the fetal femur length determined by an ultrasound examination in early pregnancy is, on average, shorter in fetuses with Down's syndrome than in unaffected fetuses (Benacerraf *et al.* 1987; Lockwood *et al.* 1987). Later two more studies were reported that showed no such difference (Porto *et al.* 1988; Sacks *et al.* 1988) and a third showed a difference in only one of three gestational age subgroups (Platt *et al.* 1988).

If the original observation were confirmed it would have important implications since it would mean that antenatal screening for Down's syndrome using maternal age determination and serum testing (Wald *et al.* 1988) might be improved by incorporating fetal femur length as an ancillary screening variable. The present study was carried out to investigate this further.

Subjects and methods

Two series of pregnancies associated with fetal Down's syndrome were identified: (1) an antenatal series: 76 detected antenatally in 1986–89 by amniotic fluid karyotypes performed in six cytogenetics laboratories in Greater London; and (2) a birth series: 109 recognized through the birth of an infant with Down's syndrome in 1986–88 that had a karyotype performed at the North East Thames Regional Cytogenetics Unit. Information was sought from the medical records relating to these 185 affected pregnancies to determine whether a femur length and biparietal diameter (BPD) measurement had been made and if so in which ultrasound department. To allow for systematic differences in technique between ultrasound departments,

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each department concerned was asked to provide pairs of femur length and BPD measurements on 50 pregnancies either abstracted at random from the department's records, or a consecutive series of data collected specially (hereafter referred to as 'control pregnancies'). Affected pregnancies were only included if the femur length and BPD measurements had been made at the same examination and before the fetal karyotype was known. If more than one pair of femur length and BPD measurements were available from a pregnancy, only the first was used.

Data were available for 83 affected pregnancies (50 from the antenatal and 33 from the birth series). Gestational age ranged from 13 to 39 weeks and in all but five the measurements were made during the second trimester. The 27 ultrasound departments where the measurements had been made were able to provide usable data on 1340 controls (information on a further ten controls from six hospitals was incomplete). Ultrasound technique varied considerably: 18 departments measured BPD from the outer to inner cranial edge, nine from outer to outer; 17 measured femur length from the greater trochanter to the femoral diaphysis, nine measured the calcified part, one did both depending on gestation; 14 reported the mean of more than one femur measurement, 13 reported the longest measurement; eight used only a linear array transducer, four only a curvilinear array, two only a mechanical sector, 13 used more than one type of transducer; and there was a wide variation in practice regarding the inclination of the transducer when imaging the femur.

A linear regression analysis was performed of femur length on BPD for pairs of values from control pregnancies from each ultrasound department. This was used to estimate the expected femur length for a given BPD at each department. The expected femur length for a BPD of 30 mm (equivalent to a gestation of approximately 15 weeks) ranged from 14 to 19 mm (median 16 mm), for a BPD of 50 mm (20 weeks) it ranged from 33 to 36 mm (median 34 mm) and for a BPD of 70 mm (27 weeks) it ranged from 49 to 54 mm (median 51 mm). In the data from some centres there was a statistically significant deviation from linearity but this was not large enough to justify a more complex regression. Femur lengths in affected and control pregnancies were then expressed as multiples of the expected for the relevant BPD and for the ultrasound department concerned. Since the BPD is similar in pregnancies with Down's syndrome compared with unaffected pregnancies (Cuckle & Wald 1987; Lockwood *et al.* 1987) this method is an accurate way of allowing for gestational age.

Results

The median fetal femur length in the 83 pregnancies with Down's syndrome was 0·94 times the expected value (95% CI 0·92 to 0·96)—a statistically significant reduction from 1.00 ($P<0·0001$).

Table 1 shows for affected and control pregnancies, the median and the 25th and 75th centiles of the femur length expressed as a multiple of the expected, according to BPD and maternal age. There is no suggestion that the extent of reduction in femur length in affected pregnancies (or the scatter of values) is related to BPD (and hence to gestational age), or to maternal age.

Table 2 and Fig. 1 show that there is substantial overlap in the distributions of femur length values in affected and control pregnancies. Nonetheless, cut-off levels can be chosen which identify a group of pregnancies with a high relative risk of Down's syndrome. For example, 11% of affected and 1·4% of control pregnancies had femur lengths ≤0·85 times the expected—a seven to eightfold increase in risk.

The distribution of femur length expressed as multiples of the expected is approximately Gaussian in both affected and control pregnancies over a wide range of values, but there are insufficient data to judge the fit outside the range 0·80–1·20 times the expected. This is illustrated in Fig. 2, a probability plot of the data from affected and control pregnancies in which the straight lines represent Gaussian distributions with means of 0·942 and 0·999 (the medians to three decimal places) and SDs of 0·080 and 0·062 (the interval between the 10th and 90th centiles divided by 2·563) respectively.

There is statistically highly significant heterogeneity between ultrasound departments in femur lengths expressed as multiples of the expected, specifically in the median value in Down's syndrome pregnancies ($P<0·001$) and in the scatter of values in both Down's syndrome and control pregnancies ($P<0·001$). Analysis of variance was used to determine whether the differences in scatter were related to the ultra-

Table 1. Femur length expressed as a multiple of the expected value for the biparietal diameter (BPD) and relevant ultrasound department according to BPD and to maternal age

	Down's syndrome			Control pregnancies		
	n	Median	(25–75th centile)	*n*	Median	(25–75th centile)
BPD (mm)						
≤35	21	0·95	(0·90–1·02)	136	1·01	(0·96–1·05)
36–40	24	0·94	(0·90–0·99)	332	0·99	(0·95–1·03)
41–45	16	0.92	(0·90–0·98)	389	1·00	(0·96–1·04)
≥46	22	0.96	(0·91–0·98)	483	0·99	(0·96–1·03)
Maternal age (years)*						
≤24	6	0.91	(0·87–1·04)	419	1·00	(0·96–1·04)
25–9	8	0.97	(0·91–1·02)	458	1·00	(0·96–1·03)
30–4	6	0·95	(0·83–1·01)	301	1·00	(0·96–1·04)
≥35	60	0.94	(0·90–0·99)	158	0·99	(0·95–1·03)
Overall	83	0.94	(0·90–0·99)	1340	1·00	(0·96–1·04)

*Maternal age information was not available for three Down's syndrome and four control pregnancies.

sound technique used. This did not, however, provide an explanation for any of the observed differences.

Discussion

We found that the median femur length of 83 fetuses with Down's syndrome was 0·94 times the expected value for 1340 control pregnancies after allowing for gestational age (as assessed by BPD measurement) and the ultrasound department in which measurement was made—a statistically significant reduction.

The results of the six other published studies on this subject together with the present study are summarized in Table 3. The average value in affected pregnancies weighted for the number of pregnancies in each study is 0·92 times that in control pregnancies—close to our own estimate. The heterogeneity between the results from the different studies was notable (for example the difference between the New Haven and London results is statistically significant (P<0·001)) but there is no obvious explanation for this. The heterogeneity is not explained by the variety of different ultrasound techniques and equipment used since this would have influenced values in control pregnancies to the same extent as affected pregnancies. Differences in gestational age between affected and control pregnancies that may be incompletely allowed for by coarse gestational age stratification in some studies are unlikely to offer a full explanation. A possible artefact that might contribute to heterogeneity has been described (Lockwood *et al.* 1987). If in some centres ultrasonographers disregarded femur length measurements that appeared inconsistent with gestational age based on BPD (or discarded BPD estimates inconsistent with gestations based on femur length), femur

Table 2. Number and proportion of Down's syndrome and control pregnancies with femur length ≤ a given value

Femur length (multiple of expected value*)	Down's syndrome		Control pregnancies		Likelihood ratio†
	n	(%)	*n*	(%)	
≤1.00	66	(80)	701	(52)	1·5
≤0·95	44	(53)	269	(20)	2·6
≤0·90	20	(24)	84	(6·3)	3·8
≤0·85	9	(11)	19	(1·4)	7·6
≤0·80	5	(6·0)	7	(0·5)	11·5
Any	83	(100)	1340	(100)	—

*Expected value for the biparietal diameter and relevant ultrasound department.
†The number of times the risk of Down's syndrome is increased because of a reduced femur length.

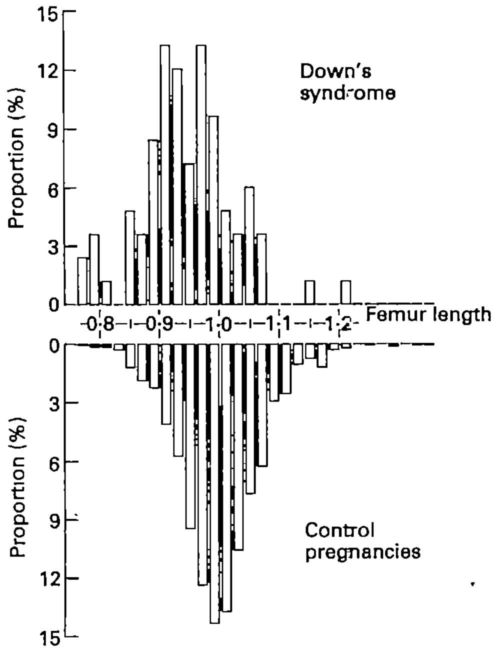

Fig. 1. Frequency distribution of femur length expressed as a multiple of the expected among 83 Down's syndrome and 1340 control pregnancies.

lengths would be artefactually increased relative to BPD in Down's syndrome pregnancies. If this happened, then studies with the smallest reduction in femur length in affected pregnancies would also have tended to have the least scatter of femur lengths in control pregnancies. We found no such association among the 27 ultrasound departments in our study, weighing against the possibility that this source of bias had an important influence.

The best way to use information on femur length in screening for Down's syndrome will be to extend the method used for serum screening in which a woman's risk of giving birth to a Down's syndrome fetus at term is estimated from her maternal age and the results of maternal serum alpha-fetoprotein (AFP), unconjugated oestriol and human chorionic gonadotrophin (hCG) tests (Wald *et al.* 1988). The method is based on estimating a woman's risk of having a Down's syndrome pregnancy and then using the risk estimate as a screening variable. The result is judged as positive if it exceeds a specified risk cut-off (say 1:200). To estimate the risk using femur length, information is needed on the extent of correlation between femur length and the serum variables but this is not available at present. Centres that have not introduced serum screening but routinely carry out a femur length measurement can improve their screening performance by estimating the risk of Down's syndrome from the maternal age and femur length alone. Since these two variables are independent (see Table 1) and the distribution of femur length is Gaussian over a range of about 0·80–1·20 multiples of the expected, a guide to risk for a value in this range would be to multiply the age-specific risk (using Table 1 in Cuckle *et al.* 1987) by a likelihood ratio. This is given by the formula for the ratio of the heights of Gaussian distributions for affected and unaffected pregnancies (see Appendix I of Cuckle *et al.* 1987) with means 0·942 and 0·999 and SDs 0·080 and 0·062 respectively, which reduces to:

$$\exp\,[51{\cdot}95\,x^2-112{\cdot}70\,x+60{\cdot}23]$$

where x is the femur length in multiples of the expected (for values outside the range 0·80–1·20 the risk will be more extreme than that at the end points of the range). For example, a 35-year-old woman has a 1:384 chance of having a Down's syndrome term pregnancy; if the femur length were 0·87 (likelihood ratio = 4·5) the risk would be increased to 1:85 (4·5×1:384), whereas if the femur length were 1·13 (likelihood ratio = 0·46) the risk would be reduced to 1:835 (0·46×1:384).

Combining information on femur length and maternal age in this way and choosing a risk cut-off to yield a 5% amniocentesis rate, the Down's syndrome detection rate will increase to 35%

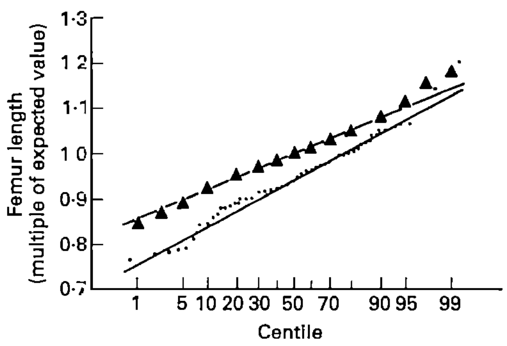

Fig. 2. Probability plot of centiles of femur length expressed as a multiple of the expected among 83 Down's syndrome (●) and 1340 control pregnancies (▲). Only selected centiles are shown for the control pregnancies.

Table 3. Mean or median femur length (FL) in Down's syndrome and control pregnancies in six studies*

Study (see footnote for references)	Measure of femur length	Mean or median femur length* (*n*)			
		Down's syndrome (a)	Control pregnancies (b)	Ratio (a)/(b)	(95% CI)
Boston (1)	Multiple of expected†	0.88 (28)	1·00 (192)	0·88	(0·84 to 0·91)
New Haven (2)					
(i) 16–17 weeks	FL (mm)	18·7 (13)	21·3 (172)	0·88	(0·81 to 0·95)
(ii) 17·5–18·5 weeks		23.3 (10)	25·9 (79)	0·90	(0·82 to 0·97)
(iii) 20–21 weeks		29·9 (10)	32·9 (26)	0·91	(0·85 to 0·97)
Irvine (3)					
(i) 16 weeks	FL/BPD	0·59 (25)	0·60 (95)	0·98	(0·96 to 1.06)
(ii) 18 weeks		0·64 (11)	0·65 (48)	0·98	(0·94 to 1·04)
(iii) 19 weeks		0·68 (2)	0·68 (29)	1·00	NC
Detroit§ (4)	FL (mm)	25·7 (12)	25·4 (16)	1·01	(0·86 to 1.17)
Los Angeles (5)					
(i) 15–16 weeks	FL (mm)	NR	NR	NR‡	NC
(ii) 17–18 weeks		NR (37)	NR (97)	NR‡	NC
(iii) 19–20 weeks‖		27	31	0·87	NC
Charleston (6)	Multiple of expected†	0·96 (10)	0·97 (74)	0·99	(0·89 to 1.03)
Present study	Multiple of expected†	0·94 (83)	1·00 (1340)	0·94	(0·92 to 0·96)

*For Boston and the present study the median is shown; for the other studies the mean is shown (for Irvine the mean BPD/FL was reported and we show the inverse of this mean)

†For the relevant BPD and ultrasound department (in Charleston based on published tables, otherwise based on linear regression of data collected in the corresponding ultrasound department).

‡No statistically significant difference between (a) and (b) was reported

§Control pregnancies were reported to be of similar gestational age to affected pregnancies.

‖A statistically significant reduction in mean BPD was also reported (42 and 47 mm respectively)

NC, Not calculable from the data reported, NR, not reported; BPD, biparietal diameter.

(1) Benacerraf *et al.* (1987); (2) Lockwood *et al* (1987); (3) Porto *et al.* (1988); (4) Sacks *et al.* (1988); (5) Platt *et al.* (1988); (6) Winston & Horger (1988).

compared with 30% using age alone to select 5% of women for amniocentesis. If the reduced femur length in affected pregnancies is unrelated to the serum screening variables AFP, unconjugated oestriol and hCG (and this needs to be investigated) then the additional use of femur length would increase the detection rate to 66% compared with 61% using serum screening alone at a risk cut-off set to yield a 5% amniocentesis rate.

To enable both a femur length and BPD measurement to be used together with the results of serum screening tests for Down's syndrome and spina bifida there is merit in performing all the measurements at about 16 weeks when serum screening for spina bifida is most effective. If a 18–20 week detailed routine scan for congenital abnormalities is planned this should not replace the 16-week scan.

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Gynaecological impact of sexual and physical abuse by spouse. A study of a random sample of Norwegian women

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Summary. A sample of 150 women aged between 20 and 49 was randomly selected from the census of the city of Trondheim, Norway. Of the 131 eligible for the study, 13 refused to participate; the participating 118 women were interviewed by a gynaecologist. Detailed information about their present and previous spouse(s) and about sexual problems and gynaecological symptoms was obtained. Physical abuse by spouse had occurred in 20 (18%) of the 111 women who had ever lived in a relationship, and sexual abuse in 19 (17%). Eleven (10%) had experienced both physical and sexual abuse. A history of physical abuse with or without sexual abuse by spouse was associated with sexual problems in the present or in previous relationships. Reported abuse by spouse was also associated with a higher frequency of gynaecological symptoms at the time of interview.

The impact of physical and sexual abuse on women's health has only recently become apparent to the health professionals. The physical injuries have been well described (Brismar & Tuner 1982). Violence by a spouse may lead to serious injuries causing disability or even death (Dobash & Dobash 1978), but the effect on general health may be far more extensive than the surgical consequences. Depression, anxiety and insomnia are common problems (Goodstein & Page 1981). Chronic pain and various somatic manifestations, including gynaecological disorders, may be associated with physical and sexual abuse (Hilberman 1978; Larsson & Andersson 1988; Chez 1988; Harrop-Griffiths *et al.* 1988).

Most studies of the effect of physical and sexual abuse have been based on the victims, or on highly selected groups of patients. The present study was designed to assess how frequently physical and sexual abuse could be detected in a random sample of women, and whether a history of abuse was associated with any specific gynaecological symptoms or sexual problems.

Subjects and methods

A sample of 150 women between 20 and 49 years of age was randomly selected through the census of the city council of Trondheim. Of the 150 women originally selected, 15 had moved, one had died and two were seriously disabled. Since cultural background is known to have an influence both on the meaning of violence and on the concept of gynaecological symptoms, one Asian woman was also excluded. Of the remaining 131 women, 13 (10%) refused to participate; these

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women did not differ in age from the participants. The 118 participating women were all interviewed by one of us (B.S.). None of the women refused to answer questions about abuse, but five who reported physical abuse by spouse did not want to give a detailed description of the violence.

The women received a written invitation to participate in a study aimed at revealing a possible association between life-events and gynaecological disorders. They were informed that the study included an interview by a gynaecologist (B.S.) and an optional gynaecologist check-up. The women were interviewed at the University Hospital in an informal setting using a structured interview and an extended gynaecological history. Detailed information was obtained about their present and previous spouse(s).

To reveal the occurrence of violence by spouse, the women were asked to fill in a questionnaire which represented a modified version of the Physical Violence Index of the Conflict Resolution Techniques (Straus 1978). If a woman met the criteria of ever having lived in a physically abusive relationship (at any time having experienced a violent act by spouse more severe than slapping), she was asked if this had caused fear and anxiety in the relationship. The women were asked if they wanted to talk about these relationships, and descriptions were obtained from most of them. A spouse was defined as a man the woman either was or had been married to or cohabited with.

The introductory question most usually revealing sexual abuse was: 'Did you ever feel pressured, threatened or forced to have sex with your partner?' Those who gave a positive answer were invited to describe the event(s). The classification given by Finkelhor & Yllo (1985) was used to group the women into sexual abuse categories and they were allocated on the basis of the most severe event experienced. Women who had experienced non-violent threats were classified according to whether the spouse had been violent under other circumstances.

To obtain estimates of the frequency of the different types of abuse by spouse, abuse was related to years at risk, based on the total number of years lived in a relationship for all the women who had such an experience. The diagnosis of gynaecological disorders was based on the presence of a gynaecological symptom at the time of the interview. Women who at any time had experienced sexual problems with their spouse included those who had problems in previous relationships as well as those with problems in the present one.

The χ^2 test was used in testing for statistically significant differences between abused and non-abused women. Miettinen's test-based method was used to calculate the confidence intervals of the odds ratios (Kleinbaum *et al.* 1982).

Results

Among the 111 women who had ever lived in a relationship, 20 (18%) had experienced physical abuse and 11 (10%) both physical and sexual abuse. Physical abuse only had occurred in nine (8%) and sexual abuse only in eight (7%). Overall, 28 (25%) of the women had experienced either physical or sexual abuse or both. They described 30 spouses with whom they had lived for 1 to 19 years (mean 7·7 years); 23 (77%) of the spouses were husbands and seven (23%) were cohabitees. Four women (3·6%) had been subjected to violence within the previous year. The occurrence of abuse is also related to the number of years at risk. Both physical and sexual abuse occurred in 8·4 per 1000 woman-years, while the corresponding figures for physical abuse only and sexual abuse only were 6·8 and 6·1 per 1000 woman-years, respectively.

Table 1 shows the different types of violence according to the most severe act experienced. Being hit or beaten up were the most common acts, reported by 7% and 6% of the women respectively. Three women (3%) had been threatened or injured with a knife. Thirteen (12%) reported that the violence had caused fear and anxiety, and four women (4%) required medical treatment for injuries inflicted. Of the 186 completed pregnancies reported by the women, physical violence had occurred in six pregnancies (3%), and in an additional five pregnancies there had been threats of violence.

The severity of sexual abuse by the spouse is shown in Table 2. Most of the sexual abuse occurred within a violent relationship. Three women used the word rape in describing the assaults experienced. Ten of the women referred to repeated sexual assaults. Some of these accounts revealed extreme situations, such as that described by one woman: 'I used to be raped many times a day, also during pregnancy. But what I found most disturbing was being raped after the onset of contractions just before I had to go to the clinic to deliver the baby'.

Table 1. Severity of physical abuse reported by 111 women who had ever lived in a relationship*

	No. of women (n=111)	
	n	(%)
No violence	91	(82·0)
Hit	8	(7·2)
Kicked/bitten or hit with fists	2	(1·8)
Beaten up	7	(6·2)
Threatened with or cut by knife	3	(2·7)

*Physical abuse categorized by the most severe act experienced.

Eight women experienced sexual abuse by a non-violent spouse. Even though these women described interpersonal coercion without threats of violence, the events often had a severe impact on their well-being. 'If I did not go along with it, I was the subject of psychological torture. He wanted it many times a day, kept on and on and wanted me to do the same thing as he had seen on the video'.

Of all 118 women in the random sample, 17 (14%) suffered from one or more gynaecological symptoms at the time of interview. The symptoms included irregular vaginal bleeding, vaginal discharge, pelvic pain and more unspecified symptoms related to the genitals. Suffering from at least one gynaecological symptom at time of interview was statistically significantly associated with a history of abuse by spouse (P<0·05). Table 3 shows the estimated odds ratio and the 95% confidence interval. The sample size does not allow for more detailed analysis by separate symptoms.

Of the 111 women who had ever lived in a relationship 51 (46%) reported sexual problems in their relationships. Ever experiencing sexual and/or physical abuse by the spouse was statistically significantly associated with a positive history of sexual problems (P<0·001). The type of problems reported were related to lack of libido, difficulty in achieving orgasm, and problems caused by conflicts over sexual frequency. As shown in Table 3, the estimated odds ratio of abuse history in women with sexual problems is 9·1 (95% CI 3·27 to 25·51).

Table 2. Severity of sexual abuse reported by 111 women who had ever lived in a relationship

	No. of women (n=111)	
	n	(%)
No sexual abuse	92	(82·9)
Coercion by non-violent spouse	8	(7·2)
Threats or use of violence	8	(7·2)
Rape	3	(2·7)

Discussion

The definition of what constitutes physical and sexual abuse by a spouse has been under debate. For a woman to be classified as being the victim of physical abuse by her spouse, a history of more than one violent episode causing visible injury has been used as a criterion (Gayford 1975). Other researchers have based their classification on the behavioural dynamics within the violent relationships (Walker 1979). Violence causing fear and anxiety has also been used as an indication of abuse. Sociological studies use the severity of the act to determine what constitutes wife beating (Straus 1978). In the present study, physical abuse has been defined according to the severity of the violent act. Women subjected to less severe acts, such as being pushed around, grabbed or slapped by the spouse have not been included. All of the 15 women who gave detailed accounts of the abuse reported severe or repeated injurious assaults and would be defined as being the victims of physical abuse by any classification.

Few population-based studies focusing on physical abuse by the spouse have been reported. The estimate of recent physical abuse obtained in the present study is in accordance with the results from an American population-based study, which found that 3·8% had experienced physical abuse by the spouse within the previous year (Straus 1978). Our finding that at

Table 3. Odds ratios of history of physical and/or sexual abuse by spouse in women with gynaecological symptoms at time of interview and those with a history of sexual problems

		History of abuse		
Patient group	n	n	(%)	Odds ratio (95% CI)
Gynaecological symptoms	17	8	(47)	3·6 (1·11–11·67)
Sexual problems	51	23	(45)	9·1 (3·27–25·51)

least 13% of all the women who had ever lived in a relationship had been physically abused is in accordance with the results from a population-based study in New Zealand by Mullen *et al.* (1988) who found that 10% of their women had experienced repeated battering and in 4% the battering required medical attention.

Sexual abuse by the spouse was first described among women who were known to be victims of physical abuse (Hilberman 1978). Two population-based studies have reported frequencies of 10% (Finkelhor & Yllo 1985) and 14% (Russel 1982) of sexual abuse by the spouse. Both these figures are lower than the 17% found in our study. These differences may be real but could also be due to different methodology. If only sexual activity under direct or indirect threats or the actual use of physical force are included, the proportion in the present study is reduced to 10%.

Severe violence in pregnancy constitutes an obvious risk for the woman and her fetus. Miscarriages attributed to violence have been reported (Fagan *et al.* 1983; Hillard 1985), as well as perinatal death (Morey *et al.* 1981). The reported frequency of violence in term pregnancy of 3% in our study is in accordance with the only prospective study directly addressing this issue (Hillard 1985).

The apparent association in our study between a history of abuse by the spouse and sexual problems might be a consequence of the need of these women to find a cause for their sexual problems. Another possibility is that women who have experienced abuse could be more prone to recall sexual problems. Both these possibilities are likely to play a part, but we doubt if they fully explain the associations. Studies of women raped by someone other than their spouse have shown that the long-term traumatic effects include sexual difficulties (Burgess & Holmstrom 1974). Psychological studies show that being sexually assaulted by a trusted person brings out other kinds of negative emotional reactions in addition to the effects seen after rape by a stranger (Shields & Hanneke 1983). These findings support the assumption that the association observed between the history of sexual and/or physical abuse, and sexual problems is likely to be causal.

Our finding of an association between gynaecological symptoms and violence by spouse involved a cross-sectional study, which means that the time sequence between the abuse and gynaecological symptoms is uncertain. Although it seems likely that the gynaecological pathology is a consequence of the abuse, it might be argued that women with gynaecological disorders are more prone to enter abusive relationships or that gynaecological symptoms create situations in which abuse is more likely to occur.

The association between abuse and gynaecological symptoms might involve psychological factors. Gynaecological patients were reported to have a generally higher level of psychiatric morbidity (Byrne 1984), and a community-based survey showed that psychiatric morbidity was associated with gynaecological symptoms (Gath *et al.* 1987). Since either physical or sexual abuse by a spouse is known to cause a higher level of psychopathology (Mullen *et al.* 1988), it is reasonable to believe that sexual and physical abuse by the spouse can result in a higher frequency of psychopathology in these women.

With regard to specific gynaecological symptoms, bleeding disorders are known to be associated with psychiatric morbidity, particularly depression (Greenberg 1983), and the latter is regarded as one of the major psychological reactions to living in an abusive relationship.

A higher frequency of genital infections among abused women is also likely to contribute to the generally higher gynaecological morbidity in this group. Battered women often report their spouse to be indulging in extramarital sex so exposing them to an increased frequency of sexually transmitted diseases (Hilberman 1980). Violent sexual activity might also cause tissue damage and this may facilitate infections with endogenous flora (Lee *et al.* 1988).

Most likely, pelvic pain is one of the conditions that contributes to the generally higher gynaecological morbidity among abused women. Pelvic pain is known to be associated with recent experiences of life stress (Beard *et al.* 1988). There are no studies directly addressing the question of whether abuse by a spouse might be one of the stress factors, but 'serious difficulties in the relationship with husband or lover' (Beard *et al.* 1977) has been reported as an important associated factor.

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Characteristics of persistent ovarian masses in asymptomatic women

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Summary. Persistent ovarian masses have been found in a substantial proportion of 5479 self-selected asymptomatic women who were screened for early ovarian neoplasia. Each woman was scheduled to undergo three ultrasound screens (consisting of 1–12 scans) to detect regressing and non-regressing masses. A total of 14,594 screens (15,977 scans) was performed. The average interval between successive screens was 595 days (range 214–1134 days). Overall, 650 screens (4·4%; 10·1% of women) produced a positive result which became negative with successive scans (four times more frequently in pre- than naturally postmenopausal women), and 338 screens (2·3%; 5·9% of women) had a final positive result (at least one ovary that was grossly abnormal or contained a persistent mass). Biopsies were taken from 336 ovaries (89% of total, 271 women). Overall, 134 tumour-like conditions and 119 benign tumours were identified. The detection rate of tumour-like conditions was 1·5 times higher in premenopausal than naturally postmenopausal women, whereas the proportion of tumours to normal ovaries was similar in both groups. Overall, 51% of tumour-like conditions and 70% of all tumours were detected at screen 1. Four women had metastatic ovarian cancer (three at screen 1, one at screen 2; two were bilateral). Five women (0·1%) had a primary malignant tumour (two at screen 1, three at screen 2; four were stage 1a and one was stage 1b). All women are being monitored to obtain additional information about the significance of the findings.

The important and expanding role of ultrasonography in gynaecological practice has been reviewed (Goswamy 1987). The technique was used initially to investigate overt abdominal swellings (Donald *et al.* 1958; Donald 1963), and subsequent results showed that a useful distinction could be made between predominantly cystic or solid lesions (Reeves *et al.* 1980). The

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advent of real-time sector scanners enabled the inspection and measurement of follicular growth (Hackeloer *et al.* 1979; Sallam *et al.* 1982) and provided additional evidence for the occurrence of ovulation (Queenan *et al.* 1980). The improved resolution has also been used to diagnose and determine the prevalence of polycystic ovaries (Polson *et al.* 1988).

During the last 8 years we have been developing and assessing a screening procedure that involves the use of ultrasound for the detection of early ovarian neoplasia in asymptomatic women. Initially we showed that real-time ultrasonography could be used to determine ovarian size and abnormal morphology in women who were >44 years old (Campbell *et al.* 1982; Goswamy *et al.* 1983). Subsequently we started a large prospective study designed to assess the usefulness of the screening procedure and obtain more information to refine the criteria for a definitive result. Recently we published a detailed analysis of factors that affect normal ovarian size in postmenopausal women (Goswamy *et al.* 1988). Over 5000 women have been studied and the present report describes a histological classification of the ovarian masses that were found. The prevalence of each type of abnormality is related to the time of three successive screening procedures and the menopausal state of the women.

Subjects and methods

The aim was to screen at least 5000 asymptomatic women (>44 years of age) annually for 3 years for early ovarian cancer. Those women with a gross ovarian abnormality, or a persistent pelvic mass, were to be informed about the nature and significance of the findings. The information was also sent to the appropriate general practitioner with a recommendation that the patient should be referred for further investigations. The protocol was approved by the ethics committee at King's College Hospital.

The women were self-selected in that they responded to advertisements placed within King's College Hospital, or in the local or national press. The women were ascertained to be either premenopausal (a menstrual period within the previous 12 months), artificially postmenopausal (due to hysterectomy, and in one case radiation therapy) or naturally postmenopausal (age >35 years, and at least 1 year since the last menstrual period). A total of 5479 women was recruited. Their mean age was 52 years (range 18–78); 224 women below the age of 45 years were also screened because they had a personal or family history of cancer. Initially 45% were premenopausal, 12% had undergone an artificial menopause, and 43% were postmenopausal. One woman (age 48 years) did not have a uterus at birth and possessed only one ovary which was normal. A change in the menopausal state of any woman at each screen was recorded.

Screening procedure

The screening procedure (screens 1–3) consisted of a number of ultrasound scans. Two outcomes were possible at screen 1 scan 1: negative (both ovaries normal) or positive (at least one ovary abnormal). According to the protocol all women with a positive result were invited to return for additional scans (at intervals of approximately 6 weeks) until short-term changes in ovarian morphology or volume were excluded and a test result was obtained. In practice there were three possible outcomes from scan 2 to the penultimate scan: negative, positive, or repeat (unclear). At the final scan (or from a follow-up of non-attendance) a final decision was made about the screen result. All women with a negative result were invited to attend for screens 2 and 3. Those patients with a positive result, but at least one remaining ovary after further investigation and treatment, were also invited to attend for successive annual screens. We performed 14,594 screens (15,977 scans) and examined 29,140 ovaries.

All women attending the clinic were instructed to drink more than 1 litre of fluid 1 hour before each scan. The full bladder displaces the intestinal loops and enhances the view of the pelvic organs (Donald 1963).

Normal ovaries (giving a negative scan result) are ovoids with regular outlines and low, uniform echogenicity like the uterus (Goswamy 1987). Transverse and longitudinal scans were performed to determine ovarian size (Goswamy *et al.* 1988). The maximum transverse, antero-posterior and longitudinal diameters (D_1, D_2 and D_3) of each ovary were measured and the volumes calculated according to the formula:

$$\text{Volume} = (\pi/6) \times D_1 \times D_2 \times D_3$$

An abnormal ovary (giving a positive scan result) either had an irregular outline, or a unilocular or multilocular cyst (giving very low echogenicity) with or without solid areas (Goswamy *et al.* 1983; Goswamy 1987). An overtly enlarged ovary (volume >20 ml) also suggested the presence of an ovarian mass. All scans were performed with a mechanical sector scanner (Diasonics DRF 100) from Sonotron Ltd, Bedford, UK, by one of three ultrasonographers.

Histopathology

Tissues from abnormal ovaries were examined at the referral hospitals, and detailed reports were sent to the ovarian scanning clinic. The masses were mainly classified according to criteria recommended by the World Health Organization (Serov *et al.* 1973). The groups were common epithelial tumours, sex cord stromal tumours, germ cell tumours and tumour-like conditions. The main subdivisions of common epithelial tumours were labelled as serous, mucinous, endometrioid or clear cell. The tumours were also classified as benign, borderline, or malignant. The tumour-like conditions were subclassified as simple cysts, solitary follicle cysts, corpus luteum cysts, surface epithelial inclusion cysts or parovarian cysts. We were unable (from the pathology reports) to differentiate between endometriosis (a tumour-like condition) and an endometrioid tumour. Accordingly all such conditions were classified as endometrioid tumours for this analysis. The stage of each primary ovarian cancer was determined from the operation report according to the revised recommendations of the International Federation of Gynaecologists and Obstetricians (Creasman 1987). At stage 1a the tumour was limited to one ovary and the capsule was intact. There was no tumour on the external surface of the ovary and no ascites was present. At stage 1b the same criteria applied to both ovaries.

Data base and statistical analysis

A data base was established using FoxBase running on an IBM PC/XT compatible microcomputer with a hard disc. A tape streamer was used for data back-up. A suite of programs was developed to facilitate data entry, checking and retrieval.

Results

The number of women studied at each screen, and the number and proportion with a defined outcome are listed in Table 1. It may be calculated that 90% of the women attended for screen 2 and 77% for screen 3 giving a total of 14 594 screens. Initially 335 screens (6·1% of 5479) were positive. The ratio of initially positive/finally negative to initially positive/finally positive results was 0·7, 2·7 and 5·2 at screens 1, 2 and 3 respectively. In addition, the proportion of positive/negative to positive/positive results was similar in premenopausal women and those who had undergone an artificial menopause, but was approxiamtely four-fold higher than in naturally postmenopausal women. Overall, 4·4% of screens (654) gave a positive/negative result, and 2·3% (338) gave a positive/positive result. The corresponding values per woman were 10·1% (575) positive/negative and 5·7% (326) positive/positive.

Most women (4061) had a negative result at all three screens, 639 had two negative results followed by non-attendance and 453 had one nega-

Table 1. The number of women with a defined result at each screen

Screen no.	No. of women	Result (initial/final)* (Neg./—) *n*	(%)†	(Pos./neg.) *n*	(%)†	(Pos./pos.) *n*	(%)†
1	5479	5145	(93·9)	139	(2·5)	195	(3·6)
2	4914	4568	(93·0)	254	(5·2)	92	(1·9)
3	4201	3889	(92·6)	261	(6·2)	51	(1·2)
All Screens	14 594	13 602	(93.2)	654	(4·4)	338	(2·3)

* The same women may have a positive result at more than one screen.
† Of total women at each screen.

Table 2. The number of ovaries at each screen with masses classified by histological criteria

Classification	Screen 1	Screen 2	Screen 3	Total
Epithelial				
Benign	72	19	4	95
Malignant	3	3	0	6
Sex cord stromal	4	3	1	8
Germ cell	10	3	3	16
Metastatic tumours	5	1	0	6
Tumour-like	69	39	26	134
Unclassified*	17	14	12	43
False-positive	39	22	10	71
Total	219	104	56	379

* Mass confirmed at laparoscopy, but no biopsy taken, or woman refused further investigations.

tive result followed by two non-attendances. Sixty-four women had a positive result followed by two non-attendances and a further 58 were positive at the second screen followed by a non-attendance. Forty-five women were positive at the third screen. Twelve women were positive at screen 1 and negative at screen 2 (i.e. the remaining ovary was normal). Twelve women had a positive result at more than one screen.

The median interval between the final scan at any screen and surgery was 48 days (range 12–191 days). Most women (297) with a positive screen result had a mass on one ovary only, and these were about equally distributed between the left (152) and right (145) sides of the body. There were 41 patients with bilateral ovarian masses. Biopsies were taken from 336 ovaries after oophorectomy (i.e. from 89% of the total observed at laparotomy).

Masses by screen

The mean interval between screen 1 and screen 2 was 614 days (range 289 to 1134 days). The

Table 3. A subdivision of the ovarian tumours by screen according to criteria recommended by the WHO

Type of tumour	Screen 1	Screen 2	Screen 3	Total
Epithelial				
Serous				
Benign	31	9	3	43
Borderline/malignant	2	1	0	3
Mucinous				
Benign	17	0	0	17
Borderline/malignant	0	1	0	1
Endometrioid				
Benign	24	10	1	35
Borderline/malignant	0	1	0	1
Clear cell				
Malignant	1	0	0	1
Sex cord stromal				
Thecoma	0	1	0	1
Fibroma	4	2	1	7
Germ cell				
Mature	10	3	3	16
Metastatic	5	1	0	6
Totals	94	29	8	131

Table 4. The menopausal status of women at each screen

Menopausal status	Screen 1 n	(%)	Screen 2 n	(%)	Screen 3 n	(%)	Total no. screens
Pre.	2470	(45)	1778	(36)	1185	(28)	5433
Post. (artificial)	662	(12)	632	(13)	571	(14)	1865
Post. (natural)	2346	(43)	2503	(51)	2444	(58)	7293
Missing*	1	—	1	—	1	—	3
Totals	5479	(100)	4914	(100)	4201	(100)	14 594

* Congenital absence of uterus.

corresponding interval between screens 2 and 3 was 564 days (range 214 to 1019 days). The overall mean between screens was 595 days (range 214 to 1134 days).

The number of ovaries with different types of masses at each screen is shown in Table 2. Most masses were either tumour-like conditions (35%) or benign epithelial tumours (25%). There was a marked decrease in the proportion of benign epithelial tumours to normal ovaries by screen (1·3%, 0·4% and 0·1% respectively). Sex cord stromal tumours only occurred unilaterally.

A subdivision of the tumours by screen according to the WHO criteria is shown in Table 3. Four of the six malignant ovarian tumours (five women, four stage 1a, one stage 1b) were borderline; three of these tumours were detected at screen 1 and three at screen 2 (two women at screen 1, three at screen 2). One of the women with a malignant tumour (borderline endometrioid; stage 1a) detected at screen 2 had already had one ovary (containing endometrial-like cells) removed after screen 1. The other borderline stage 1a tumours were classified as a mucinous cystadenocarcinoma and a serous papillary cystadenocarcinoma. The fourth stage 1a tumour was a clear-cell carcinoma. The stage 1b tumours were serous borderline cystadenocarcinomas.

Most tumour-like conditions were simple cysts (43%): 30 at screen 1, 15 at screen 2 and 12 at screen 3. There were 21 follicular cysts at screen 1, 11 at screen 2 and three at screen 3. There were eight corpus luteum cysts at screen 1, six at screen 2 and five at screen 3. The remaining masses were either surface epithelial inclusion cysts (total 9) or parovarian cysts (total 14).

Table 5. The number of ovarian masses in women classified by menopausal status

Classification	Pre. n	(%)*	Post. (artificial) n	(%)*	Post. (natural) n	(%)*	Total
Epithelial							
Benign	38	(0·7)	20	(1·1)	37	(0·5)	95
Malignant	1		0		5		6
Sex cord stromal	1		3		4		8
Germ cell	9		0		7		16
Metastatic	2		3		1		6
Tumour-like	61	(1·1)	22	(1·2)	51	(0·7)	134
Unclassified†	17		6		20		43
Total	129	(2·4)	54	(2·9)	125	(1·7)	308

* Of total number of screens.

† Mass confirmed at laparoscopy, but no biopsy taken, or subject refused further investigations.

Masses by menopausal status

The number of women at each menopausal state at successive screens is shown in Table 4. There was an overall decrease of 52% in the number of premenopausal women and a slight increase (4%) in the number of postmenopausal women.

The number of ovarian masses associated with each menopausal state is shown in Table 5. The proportion of women with persistent ovarian masses was higher in the premenopausal group and in those who had experienced an artificial menopause. However, an additional analysis showed that there was only a small change in the proportion of ovaries with tumours or tumour-like conditions with age. Thus the odds of finding an ovary with a tumour (benign, borderline, or malignant) in the age group 45–54 years were 1 to 207, and for a tumour-like condition 1 to 189. The corresponding figures for the age group 55–64 years were 1 to 301 and 1 to 293 respectively.

Tumours by screen and menopausal status

The number and percentage of women with an ovarian tumour at different screens and by menopausal state is shown in Table 6. It may be calculated that >70% of tumours were detected at the first screen. In addition, there is a similar detection rate in premenopausal women and those who had undergone a natural menopause. The prevalence of epithelial tumours was about twice as high in women who had undergone an artificial menopause compared with the other groups.

About 51% of tumour-like conditions were detected at the first screen (89/134), 29% at screen 2 (39/134) and 19% (26/134) at screen 3. There was a greater chance (approximately 1·5-fold) of finding a tumour-like condition in premenopausal women compared with naturally postmenopausal women (see Table 5).

Discussion

The establishment of an ultrasound-based screening procedure for the detection of early ovarian cancer has enabled us to study the prevalence of regressing and non-regressing ovarian masses in self-referred asymptomatic women mostly over the age of 44 years. Data on 55 variables were collected, and an analysis of the characteristics of the self-selected sample of women presenting for the screening procedure indicated that it was similar to the general population of comparable age. This conclusion was reached after comparing the distribution of variates for social class, marital status, parity and history of infertility with the corresponding figures for the general population, according to the Office of Population Censuses and Surveys, over the period of the study. There are, however, some difficulties in the interpretation and presentation of the ovarian data. For example, many of the women had to travel long distances

Table 6. The number and percentage of women with ovarian tumours by screen and menopausal status

	Menopausal status							
	Pre.		Post. (artificial)		Post. (natural)		Total	
Screen	*n*	(%)*	*n*	(%)*	*n*	(%)*	*n*	(%)*
Epithelial								
1	32	(1·3)	15	(2·3)	28	(1·2)	75	(1·4)
2	6	(0·3)	5	(0·8)	11	(0·4)	22	(0·5)
3	1	(0·08)	0	(—)	3	(0·1)	4	(0·1)
Subtotal	39		20		42		101	
Sex cord stromal, germ cell								
1	7	(0·3)	2	(0·3)	5	(0·2)	14	(0·3)
2	0	(—)	1	(0·2)	5	(0·2)	6	(0·1)
3	3	(0·3)	0	(—)	1	(0·1)	4	(0·1)
Subtotal	10		3		11		24	

* Of total women in each group.

to the ovarian scanning clinic, and some underwent laparoscopy and/or laparotomy, and unilateral or bilateral oophorectomy as a consequence of the screen results. For these and other reasons, 13% of the women did not attend for screen 2, and 23% for screen 3. In addition, 12 women had a positive result at more than one screen, and 41 patients undergoing surgery had bilateral ovarian masses with different histological appearances.

The difficulties of classifying ovarian masses, even within one centre, are well known, and the problem was exacerbated in the present study since the pathology reports were obtained retrospectively from the hospitals to which the patients were referred by their general practitioner. In particular, it was difficult for us to classify patients as either having an endometrioid tumour, or an endometriotic cyst (a tumour-like condition). For the purposes of the descriptive analysis of ovarian masses in this age group, all such cases were classified as endometrioid tumours, which will have a definite but unknown effect on the actual proportion of total tumours to tumour-like conditions. The appearance of different types of masses under ultrasound has been described previously (Bhan & Campbell 1986).

Marked changes in ovarian structure and function are known to occur during the climacteric. Accordingly we decided that it was appropriate to classify the women as premenopausal, artificially postmenopausal or naturally postmenopausal. Obviously the menopausal status of many women changed during the course of the study. From the analysis of menopausal status it was apparent that many of the women who did not attend for screen 3 were elderly and in the postmenopausal group. Thus the type, number and proportion of each ovarian mass was related by ovary to the screen number and the menopausal status of the woman at the time the screen result was obtained.

After the three screens we were surprised to find that approximately 16% of women had a result that was initially positive. Of these 10% were eventually classified as negative after repeat scans (i.e. the women had regressing tumours). However, 5·9% either had a grossly abnormal ovary (approximately 18% of women with a positive result only had one scan), or at least one non-regressing mass. The ratio of initially positive/finally negative results to initially positive/finally positive results increased progressively at screens 2 and 3 and this finding probably reflects a reduction in the type of ovarian pathology due to previous interventions, or to the experience gained by the ultrasonographers. The finding that the proportion of initially positive/finally negative results was approximately four times higher in premenopausal women is consistent with cyclic ovarian activity in this group. It is also interesting that 41 women out of 338 with a final positive screen result had an apparent mass in both ovaries. As expected, single masses were equally distributed between the left and right ovaries. There was only a slight reduction in the proportion of women with tumours or tumour-like conditions with age.

Most of the classified masses were either tumour-like conditions (35%) or benign epithelial tumours (25%). The prevalence of benign epithelial tumours decreased markedly by screen, and they were predominantly classified as serous, endometrioid or mucinous. Epithelial tumours constituted 73% of the benign masses, and 100% of the primary ovarian cancers. These proportions are similar to those reported previously for symptomatic women (Scully 1977). Most of the tumour-like conditions were simple cysts (43%). It was of particular interest that 74% of the tumours were detected at the first screen. Moreover, the detection rate was similar in premenopausal women and those who had undergone a natural menopause. We also found that the risk of developing a tumour was two-fold higher in women who had undergone a hysterectomy (i.e. the artificial menopause group). More data about these women will be presented in a further publication. Only 50% of the tumour-like conditions were detected at the first screen and proportionately more were found in premenopausal women.

Four metastatic carcinomas were detected: three at screen 1 and one at screen 2. One of these women was premenopausal, two were artificially menopausal and one was postmenopausal. Five primary ovarian cancers were detected. One woman was premenopausal (age 46 years) and four were postmenopausal. There are insufficient numbers to interpret these findings. The significance of finding many asymptomatic women with persistent tumour-like conditions or benign tumours remains to be determined. However, the prevalence of ovarian neoplasms and functional ovarian cysts, as detected at laparotomy or laparoscopy, in a large cohort of women has been related to the intake of combined oral contraceptive tablets and parity (Vessey *et al.* 1987). It has also been suggested that malignant tumours may arise from benign and borderline masses as well as from healthy tissues (Colgan & Norris 1983; Yoonessi *et al.* 1988). If this proposition were to be substantiated and quantified by a prospective controlled clinical trial of an ultrasound-based screening procedure then the present findings could be extremely important. The detection and false-positive rates of the screening procedure for primary ovarian cancer and for ovarian masses, and the development of new screening strategies, are the subjects of separate publications.

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The effect of anorexia nervosa on skin thickness, skin collagen and bone density

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Summary. The effects of anorexia nervosa on skin thickness, skin collagen content and bone density were investigated in a cross-sectional study of 36 women with anorexia nervosa with a 4-year median duration of amenorrhoea and compared with a group of 33 women of comparable age without anorexia and with normal periods. The median skin thickness, assessed radiologically, was significantly reduced ($P<0·01$) from 0·88 mm in the comparison group to 0·70 mm in the anorectic group and the median collagen content was significantly reduced from 209 $\mu g/mm^2$ in the comparison group to 164 $\mu g/mm^2$ in the anorectic group ($P<0·05$). The median bone density in the comparison group was 0·93 gHA/cm^2 at the lumbar spine and 0·84 gHA/cm^2 at the proximal femur. These values were greatly reduced in the women with anorexia nervosa to 0·77 gHA/cm^2 and 0·65 gHA/cm^2 respectively ($P<0·01$). Our findings confirm the loss of bone mass with anorexia and demonstrate the coexistent loss of skin thickness and skin collagen content. This association supports the hypothesis that a generalized loss of collagen is a major factor in the causation of osteoporosis following oestrogen deficiency.

Anorexia nervosa is associated with prolonged amenorrhoea, oestrogen deficiency and severe osteoporosis (Rigotti *et al.* 1984; Biller *et al.* 1989), demonstrating many similarities with postmenopausal osteoporosis. These bone changes may be a result of either the decreased oestrogen production from the ovary or the decreased conversion of adrenal precursors to oestradiol in the diminished body fat or to the general effects of starvation. We have shown previously that postmenopausal osteoporosis is accompanied by a decrease in skin thickness and a reduction in the skin collagen content. These skin changes can be prevented or reversed with oestrogen replacement therapy indicating that sex hormones can have a direct effect on collagen metabolism (Brincat *et al.* 1985). Anorectic women have thin dry skin that bruises easily. This study was designed to investigate the effect of anorexia nervosa on skin thickness and skin collagen as well as on bone density.

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Subjects and methods

This cross-sectional study comprised 36 women with anorexia nervosa who had had amenorrhoea for a median duration of 4 years and a group of 33 female volunteers of comparable age

Table 1. Characteristics of 36 anorectic women with amenorrhoea and a comparison group of 33 women

Characteristic	Anorectic group ($n = 36$)	Comparison group ($n = 33$)
Age (years)	24 (18–48)	26 (21–46)
Weight (kg)	43 (30–56)	60 (47–87)
Height (cm)	165 (149–174)	162 (153–172)
Body-mass index	15·8 (13·1–20)	22·0 (17–27)
Duration of amenorrhoea (years)	4·0 (1–20)	0

Results are median (range) values.

without anorexia and with normal periods recruited from the nursing and medical staff of this hospital (Table 1). All the women were nulliparous. Informed consent was obtained and this study was approved by the ethics committee of King's College Hospital

The bone density of the lumbar spine and femoral neck was estimated using dual photon absorptiometry. The radioactive source utilized was gadolinium-153 and the absorptiometer was standardized with a solution radiologically equivalent to hydroxyapatite (HA) and the results were expressed as grams of hydroxyapatite per unit projected areas of bone (gHA/cm^2). The precision of this technique is 1–3% with an accuracy of 2–5%. The forearm skin thickness was estimated using a simple radiological technique developed at the Dulwich Hospital menopause clinic (Brincat *et al.* 1987). Punch biopsy specimens of skin were obtained for collagen estimation from the lateral aspect of the thigh 5 cm inferior to the greater trochanter as described previously (Brincat *et al.* 1985). Plasma FSH, LH and oestradiol levels were estimated in the anorectic women.

Results

The anorectic women had hypogonadotrophic hypogonadism with a median serum oestradiol level of 51 pmol/l (range 30–355), a serum FSH level of 2·3 iu/l (range 1–29), and a serum LH level of 2·2 iu/l (range 1–13·2).

The median bone density in the comparison group was 0·93 gHA/cm^2 in the lumbar spine and 0·84 gHA/cm^2 in the proximal femur. These measurements were significantly reduced ($P<0·01$) at both sites in the anorectic group with values of 0·77 gHA/cm^2 and 0·65 gHA/cm^2 at the spine and femur respectively. The median skin thickness in the comparison group was 0·88 mm. This was significantly reduced ($P<0·01$) to 0·70 mm in the women with anorexia. Similarly the median skin collagen content was reduced from 209 μg/mm^2 in the comparison group to 164 μg/mm^2 in the anorectic group ($P<0·01$, Table 2).

Discussion

This study demonstrates that the bone loss with anorexia nervosa is associated with thin skin and

Table 2. Bone density of lumbar spine and proximal femur, skin thickness and skin collagen content in anorectic women and a normal comparison group

Results	Anorectic group ($n = 36$)	Comparison group ($n = 33$)
Skin thickness (mm)	0·70 (0·5–0·97)*	0·88 (0·6–1·18)
Skin collagen (μg/mm^2)	164 (92–270)*	209 (120–245)
Bone density (gHA/cm^2)		
Spine	0·77 (0·58–0·95)*	0·93 (0·89–1·14)
Femur	0·65 (0·5–0·98)*	0·84 (0·73–1·1)

Results are median (range) values.
*$P<0·01$ Wilcoxon rank sum test.

reduced skin collagen content. The association of these skin and skeletal changes with greatly reduced plasma oestrogen levels is similar to the changes that occur after the menopause and suggest a common aetiology of oestrogen deficiency.

The precise mechanism by which loss of gonadal function leads to bone loss is unclear. Much work has focused on calcium and calcium-regulating hormones with confusing and often contradictory results. Albright *et al.* (1941) stressed the association of thin skin and osteoporosis in postmenopausal women and suggested that there is a generalized atrophy of connective tissue after the menopause resulting in thin skin and also osteoporosis following the reduction of the collagen component in the organic matrix of bone. We have reported previously that the decreased skin collagen and skin thickness found after the menopause in association with postmenopausal osteoporosis can be prevented and reversed with oestrogen replacement therapy as indeed may be the loss of bone density (Brincat *et al.* 1987; Savvas *et al.* 1988). These changes in skin and bone confirm that oestrogens have a direct effect on collagen metabolism and support the original hypothesis that loss of bone collagen is the primary cause of postmenopausal osteoporosis. The same reasoning applies to the osteoporosis that is a sequel to anorexia nervosa.

Other factors such as malnutrition, calcium deficiency and a type of disuse atrophy have also been implicated in the causation of the bone loss in anorexia nervosa, but the importance of these factors may be small compared with the significance of the loss of body collagen. The osteoporosis of long-term corticosteroid therapy is also associated with thin fragile skin which bruises easily. The substantial increase of bone density that occurs with oestrogen replacement therapy is believed to be the result of replacement of collagen in the bone matrix (Studd *et al.* 1989).

Bone mass can be replaced in anorectic women when weight is regained and menstruation returns (Treasure *et al.* 1987) but anorexia nervosa may run a prolonged course and we would recommend oestrogen replacement to avoid osteoporosis and its debilitating sequelae.

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The prognostic significance of the half-life of serum CA 125 in patients responding to chemotherapy for epithelial ovarian carcinoma

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Summary. Various prognostic factors were studied in 29 patients with stage III or IV ovarian cancer who responded to initial chemotherapy after initial diagnostic surgery. The half-life of CA 125 in serum during initial chemotherapy was the most important prognostic indicator for survival ($P<0 \cdot 001$) and the chance of achieving complete remission ($P = 0 \cdot 012$). A CA 125 half-life of <20 days, 20–40 days and >40 days appears to identify patients with a good, intermediate or poor prognosis, the two year actuarial survival being 76%, 48% and 0% respectively. The chance of achieving a complete remission was 15% and 67% respectively for patients with a serum CA 125 half-life of >20 or <20 days.

There is increasing interest in CA 125 as a tumour marker in ovarian carcinoma. The serum CA 125 level is elevated (>35 units/ml) in about 80% of patients with macroscopic disease after initial diagnosis (Klug *et al.* 1984; Bast *et al.* 1983); the level rises with progression of disease and falls with response to treatment to give a sensitivity and specificity of around 76–95% (Bast *et al.* 1983; Canney *et al.* 1984; Hawkins *et al.* 1989; Schwartz *et al.* 1987). A rising CA 125 level also predicts relapse for patients thought to be in complete remission (Schartz *et al.* 1987; Hawkins *et al.* 1989; Niloff *et al.* 1986).

Although patients with ovarian carcinoma respond to a variety of chemotherapeutic agents (see review by Thigpen *et al.* 1988), there are still many who, in spite of responding to chemotherapy, have a poor outlook. An early predictor of good responders would be useful so that decisions about changing treatment can be made at an early stage in an attempt to avoid problems of multiple drug resistance and unnecessary toxicity. The prognostic significance of serum CA 125 half-life has been studied by van der Burg *et al.* (1988) who found that a half-life of <20 days was a predictor for long relapse-free survival.

Patients who respond to chemotherapy are known to have a better prognosis than non-responders and there are many reliable methods which can detect the non-responders (including the failure of serum CA 125 to fall). We therefore decided to look at patients who respond to chemotherapy and to examine the prognostic significance of the half-life of serum CA 125 for a complete response and for overall survival.

Patients and methods

Patients with ovarian cancer had serum CA 125

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Table 1. Half-life of CA 125 and response status

	CA 125 half-life (days)		
Response	>20	<20	Total
Partial	17	3	20
Complete	3	6	9
Total	20	9	29

Assessing half-life <20 as a predictor of complete response: sensitivity=6/9=0·67; specificity=17/20=0·85 (Fisher-Irwin exact test); P=0·021 (two-tailed test).

measurements taken on a routine basis at outpatient appointments and admissions. The assay used was a standard commercially available kit (Compagnie Oris Industrie), but the results of the assay were not available to those treating the patients and were not used in the assessment of response or management of the disease.

The initial data recorded for each patient were stage, amount of residual tumour and amount of ascites. Patients were assessed in detail by clinical examination at each visit, by having a CT scan or ultrasound or both at least every third course of treatment, and by laparotomy or laparoscopy, if indicated, at the completion of chemotherapy. Response to treatment was assessed as a partial response (PR) if there was >50% regression of measurable disease, a complete response (CR) if there was no detectable disease present, progressive disease (PD) if a new lesion appeared or measurable disease increased by >25% and no change (NC) if there was <50% decrease and <25% increase in measurable disease.

The half-life of serum CA 125 was calculated graphically for all those patients who had at least two, and preferably more, measurements of CA 125 of >35 units/ml during treatment so that the rate of fall could be determined. The CA 125 half-life was generally remarkably constant over the first two or three courses of chemotherapy. Because of our referral pattern most patients were not treated for about one month after surgery, and caution may be needed in interpreting the initial half-life if treatment was begun earlier as the fall in CA 125 may then reflect initial surgery.

Over an 18-month period, serial serum CA 125 measurements were obtained in 53 patients who were treated with chemotherapy for the first time after diagnostic surgery. Three patients had progressive disease during initial treatment and all three had rising CA 125 values. Eleven patients were assessed clinically as having no change and in six of them the CA 125 level rose, in two the level fell with a half-life of >100 days and in the other three, levels were always so low that a half-life could not be determined. In ten other patients who responded clinically, the serum CA 125 half-life could not be determined because in six the CA 125 levels were always too low and in the other four the relevant measurements were not done. This left 29 patients who had an objective response determined clinically and in whom the CA 125 half-life could be estimated.

It is these 29 patients who are analysed further. Their initial data showed that 18 had stage III disease and 11 had stage IV disease; the amount of residual tumour was <2 cm in 8, 2–5 cm in 5 and >5 cm in 16; 13 had no ascites and 16 had ascites. They were all treated with platinum compounds (cisplatin or carboplatin), 27 received single-agent chemotherapy and the other two received an alkylator/carboplatin combination. Clinically, nine achieved a complete response and 20 only a partial response. The serum CA 125 half-life ranged from 7 to 147 days with a median of 29 days.

For analysis of the half-life/response data the Fisher–Irwin exact test was used. Further factor analysis was by stepwise logistic regression using standard statistical package (BMDP—linear regression program). For analysis of survival a Cox proportional hazard model was used (Cox 1972). The median follow-up period was 19 months. In both these models the following coding was used—stage (IV = 1, III = 0), residual tumour (>2 cm = 1, <2 cm = 0), ascites (present = 1, absent = 0).

Results

CA 125 half-life as a predictor of complete response

The patients who responded to chemotherapy were analysed by CA 125 half-life and degree of response. As shown in Table 1, patients with a half-life >20 days had only a small chance (15%) of achieving a complete response whereas for those with half-life <20 days the chance of a complete response was 67%. Of the three patients who had a complete clinical response but a CA 125 half-life of >20 days, two had died within 1 year of starting treatment. All those

Table 2. Stepwise logistic regression for predicting complete response

	Relative chance*	95% CI	*P*-value†
Univariate			
Half-life <20/>20	3·4	1·3 to 8·5	0·004
Residual			
<2 cm/>2 cm	2·7	1·1 to 6·5	0·023
Stage III/IV	0·9	0·4 to 2·0	NS
Ascites −/+	1·0	0·5 to 2·2	NS
Multivariate model			
Half-life <20/>20	2·8	1·0 to 7·4	0·2 (NS)‡
Residual			
<2 cm/>2 cm	2·0	0·7 to 5·4	

Total number of patients=29.
*Exponential of coefficient.
†*F*-test.
‡*F*-test for fitting residual disease to half-life.

who had a half-life <20 days and a complete response survived more than 1 year.

Further analyses used stepwise logistic regression to examine how CA 125 half-life compared with other known prognostic factors, stage, amount of residual disease and the presence of ascites. Univariate analysis identified half-life of CA 125 and amount of residual disease as important prognostic factors, and multiple regression analysis showed that CA 125 half-life was the most important prognostic factor for a complete response. When this is taken into account the amount of residual disease is no longer significant (Table 2). When the order was reversed and CA 125 half-life was looked at as an additional factor to residual disease then the CA 125 half-life added additional prognostic information (data not shown). The presence of ascites or the stage (all patients were stage III or IV) were not important in predicting a complete response (Table 2). Table 3 shows the chance of achieving a complete response as stratified by CA 125 half-life and amount of residual disease; because of small numbers the confidence limits are wide but it displays an interesting pattern.

Table 3. Probability of achieving a complete response

	CA 125 half-life (days)	
Residual tumour	<20	>20
<2 cm	4/5=0·8	1/3=0·33
>2 cm	2/4=0.5	2/17=0·12

CA 125 half-life as a predictor of survival in responding patients

A Cox proportional hazard model was used to analyse the factors important in predicting survival. The factors examined were stage, residual disease, presence of ascites, and half-life of CA 125 during chemotherapy. The possible effects of any subsequent treatment were ignored. Univariate analysis identified stage and CA 125 half-life as important prognostic indicators. Considering CA 125 half-life showed no clear cut-off point for good and bad survival but the survival appeared to deteriorate progressively as CA 125 half-life increased, CA 125 half-lives of 20 and 40 days provided a convenient division. The hazard ratios and their 95% CI values are given in Table 4. Both CA 125 half-life and stage were independent prognostic indicators for survival. The survival curves by CA 125 half-life and by stage are given in Fig. 1 and 2 respectively.

Discussion

Prognostic factors are important for deciding on appropriate treatment and also when to modify treatment. We confirm here the prognostic importance of the half-life of CA 125 which was shown to be important in predicting progression-free survival by van der Burg *et al.* (1988), and we have shown that a short CA 125 half-life during initial chemotherapy is a predictor both for a complete response and for prolonged overall survival.

These data are based on a small number of patients but if confirmed in larger series they suggest a way of managing patients during chemotherapy so that those with a good or bad

Table 4. Cox proportional hazard model for predicting survival

Factor	Hazard ratio	95% CI	*P*-value*
Half-life (days)			
<20	1·0		<0·001
20–40	3·7	0·7 to 20·1	
>40	27·8	4·0 to 193	
Stage			
III	1·0		0·012
IV	4·1	1·3 to 13·8	

Total number of patients=29.
*Reduction in log likelihood.

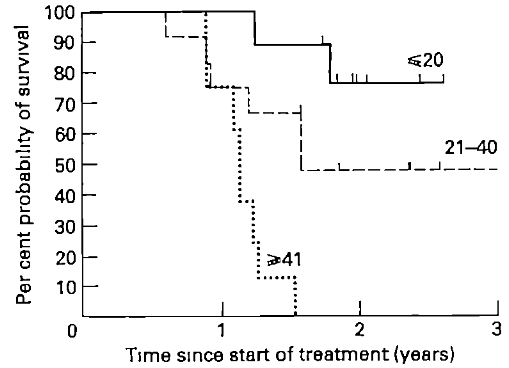

Fig. 1. Survival by CA 125 half-life. Half-life <20 days ($n=9$), 20–40 days ($n=12$), >40 days ($n=8$)

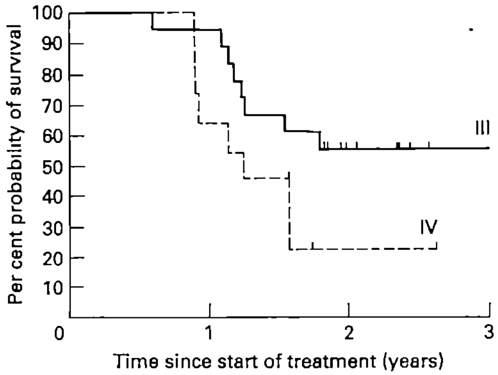

Fig. 2. Survival by stage. Stage III ($n=18$) *vs* ($n=11$). Difference is significant $P = 0{\cdot}07$.

prognosis can be identified early in treatment and appropriate changes to therapy made. An appropriate strategy in patients with raised CA 125 would be to monitor them by CA 125 measurements at the outset, and after two or three courses of treatment any with a CA 125 half-life >40 days should have their treatment modified since they would appear to have a very poor prognosis even though they may be having a minor response. Those with a half-life <20 days have a prolonged progression-free survival, a good chance of achieving a complete response and good long-term survival so they should continue with the initial therapy until CA 125 levels fall to normal and then be monitored by other means. Those with an intermediate CA 125 half-life of 20–40 days present more of a problem since we have shown that many have a reasonably prolonged survival. In these patients account could be taken of other prognostic fac-

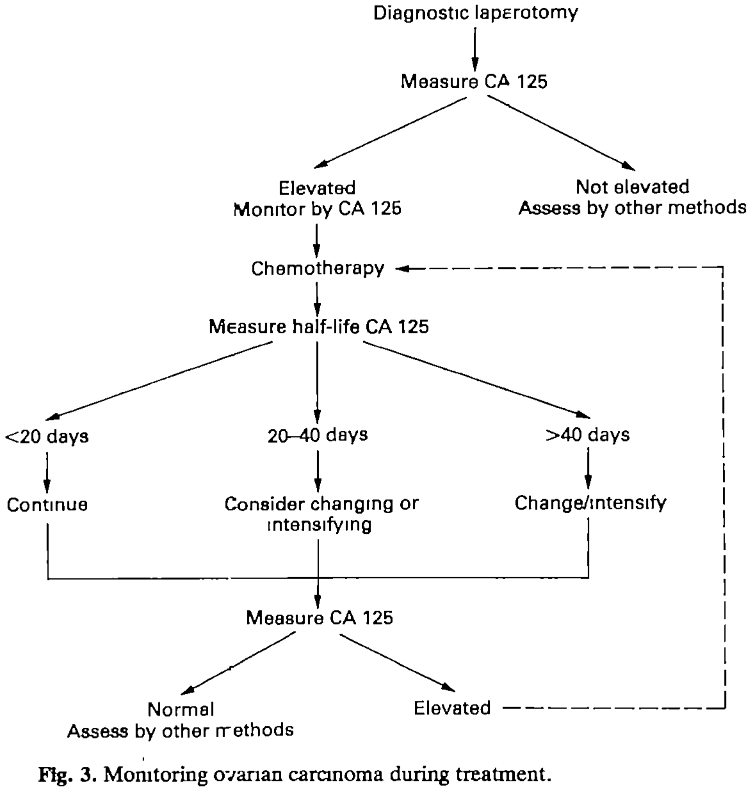

Fig. 3. Monitoring ovarian carcinoma during treatment.

tors such as stage or residual disease and apparent clinical response before deciding on treatment changes. If CA 125 fails to fall to normal it is probable that there is residual disease (Schwartz *et al.* 1987; Niloff *et al.* 1986) and treatment should continue or be modified if alternatives are available. Treatment modifications could include changes to other drugs, addition of other drugs or giving increased doses of the original drug if this is possible. This strategy is shown in the form of a flow chart in Fig. 3. Such a strategy could also be used to test new drugs in a minimum time to avoid prolonged use of a drug giving only a minor response.

Although CA 125 half-life appears to be a useful prognostic indicator for responding patients, it cannot always be determined. In the period of study we had six patients who responded clinically and yet always had low CA 125; most of them had residual disease <2 cm and it is of note that many included in this study had large residual disease. Certainly a more sensitive marker would be useful.

This strategy is strikingly similar to that used so effectively in the treatment of teratomas using alpha-fetoprotein (AFP) as a tumour marker, but it is of note that whilst in teratomas treatment produces an apparent serum AFP half-life equal to its biological half-life this is rarely the case in ovarian carcinoma (the biological half-life of CA 125 is about 5 days (Canney *et al.* 1984)). If strategies such as this are confirmed as valid in ovarian carcinoma they will also reduce the need for expensive, unpleasant scans and second-look operations. It should also be possible to adapt treatment of individual patients so that treatment that will not be of long-term benefit is modified as quickly as possible.

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Induction of labour after fetal death: a randomized controlled trial of two prostaglandin regimens

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Summary. A total of 85 women with antepartum fetal death between 14 and 42 weeks gestation was randomly assigned to one of two regimens of intravenous infusion of the prostaglandin analogue 16-phenoxy-17, 18, 19, 20-tetranor-PGE_2-methylsulphonamide (sulprostone) for inducing labour. Women received either 1 μg/min until delivery or the commonly recommended treatment of 1500 μg in 8 h followed by another, identical course of treatment if delivery did not occur within 24 h. The 1 μg/min dose schedule used half the amount of prostaglandin and resulted in statistically significantly fewer gastrointestinal side-effects compared with the conventional treatment. All women were delivered vaginally and there were no differences in induction-to-delivery intervals between the two treatments. Sulprostone infused at a rate of 1 μg/min resulted in a 50% chance of being delivered within 12 h and a 90% chance of being delivered within 24 h, with an overall frequency of side-effects of 20%.

The superiority of prostaglandins over other methods for inducing labour after antepartum fetal death before term is now well recognized (Karim *et al.* 1979; Keirse 1982; Ratnam & Prasad 1986; Tindall & Reid 1989). It is not known, however, what type of prostaglandin and what route of administration provide the best results. This is due to a lack of controlled comparisons and to the fact that the availability of various prostaglandin formulations differs from one country to another. Nevertheless, some facts have been firmly established.

It is thus known that systemic administration of natural prostaglandins in the doses needed to achieve delivery in preterm gestations results in frequent side-effects (Southern *et al.* 1978; Scher *et al.* 1980; Keirse 1982; Tindall & Reid 1989). In some countries this has led to an increasing reliance on local, mainly extra-amniotic, routes of administration (Embrey *et al.* 1974; Scher *et al.* 1980; Tindall & Reid 1989). In other countries, where prostaglandin analogues are available for systemic use, analogues have largely superseded the natural prostaglandins because of their enhanced efficacy and lower association with side-effects (Saarikoski *et al.* 1980; Keirse 1982; Ratnam & Prasad 1986; Keirse & Kanhai 1989). This trend has occurred in the Netherlands, where two prostaglandin analogues, 15-methyl-prostaglandin $F_{2\alpha}$ (Prostin M-15; Upjohn) and 16-phenoxy-17,18,19,20-tetranor-PGE_2-methylsulphonamide (sulprostone; Nalador; Schering), are available for the induction of labour after antepartum fetal death (Wallenburg *et al.* 1980; Keirse & Lobatto 1983). A comparative study between these two analogues found that sulprostone produced far fewer

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side-effects than 15-methyl-$PGF_{2\alpha}$ (Keirse & Lobatto 1983). Sulprostone therefore became the most widely used agent for inducing labour after fetal death in our country. It is also believed to be the most utero-selective stimulant among the prostaglandin analogues currently available (Hess *et al.* 1979).

Unfortunately, the dosage commonly used and recommended by the manufacturer for inducing labour after fetal death (Rizk *et al.* 1978; Schmidt-Gollwitzer *et al.* 1979; Keirse & Lobatto 1983; Kanhai & Keirse 1986) relates to experience gained in terminating second-trimester pregnancies with a live fetus. This applies to most prostaglandin regimens, but there is evidence that labour is more readily induced with prostaglandins when the fetus is dead than when it is alive (Karim *et al.* 1979; Keirse 1982; Ratnam & Prasad 1986). Our experience (Kanhai & Keirse 1986) and that of others (Fawzy & Basiony 1979; Gruber & Baumgarten 1980) suggested that lower doses of sulprostone than those commonly used did not result in a significant loss of efficacy. This is consistent with data on another analogue, which showed that halving the recommended dose did not prolong the induction-to-delivery interval after fetal death (Wallenburg *et al.* 1980).

A randomized controlled trial was therefore initiated to compare the merits and hazards of a low rate infusion of sulprostone with those of the conventional, higher dose schedule.

Subjects and methods

Nine hospitals in the Netherlands participated in this multicentre randomized controlled trial, which was approved by the ethics committee of Leiden University Hospital. It was hypothesized that, in comparison to the conventional approach, the low rate infusion would result in fewer side-effects, in shorter induction-to-delivery intervals (due to continuous rather than interrupted treatment), and in the use of fewer ampoules of the drug (lower cost). To address these questions the trial intended to recruit 80 women. Its design foresaw early completion after 50 women had been entered if major disadvantages of the new approach emerged. This was not the case and recruitment was continued until analysis of the results with the expected 80 participants allowed us to choose the better of the two treatments for all women. At that time 85 women had been entered into the trial and two of the three prior hypotheses had been answered in a statistically significant manner.

Allocation to the experimental or to the conventional treatment groups was by central telephone randomization, treatments being assigned by an envelope centrally drawn (block randomized for each participating hospital) after the name and date of birth of the women had been registered. The nature of the two treatments (8 h or continuous infusion) did not permit blinding of participating doctors and women. Women with multiple pregnancies, uterine contractions, ruptured membranes, a previous caesarean section, or a history of asthma or glaucoma were not considered eligible.

The χ^2-test was used for statistical analysis.

Table 1. Characteristics of the women entered into the trial

Characteristics of the women	Experimental treatment	Conventional treatment
No. of women	43	42
Nulliparae	23	16
Multiparae	20	26
Duration of fetal death		
Known accurately	23	23
Not known accurately	20	19
Gestation (weeks)		
Mean (SD)	27 (7)	26 (8)
Range	15–40	14–42
Duration of fetal death (days)*		
Mean (SD)	4 (5)	5 (6)
Range	1–20	1–26

* Only for women in whom the interval was known accurately

Results

The trial included 85 women with antepartum fetal death between 14 and 42 weeks gestation; they were randomized to receive either 1 μg sulprostone/min continuously (experimental treatment; $n = 43$) or three ampoules of 500 μg infused over a period of 8 h (3 μg/min; conventional treatment; $n = 42$) followed by another, identical course of treatment after 24 h if delivery had not occurred by that time. The study protocol did not direct whether and how pain relief should be given; this was left to the discretion of the clinicians at the nine participating centres. Characteristics of the women are shown in Table 1.

The total amount of sulprostone used in the experimental group was only half what was

Table 2. Amounts of sulprostone administered with two treatment regimens: (i) experimental (1 μg/min continuously), (ii) conventional (1500 μg in 8 h, repeated if necessary)

Amount of sulprostone administered	Experimental treatment	Conventional treatment
Total dose (μg) Median	720	1500
Range	240–2340	720–4500
No. of women receiving		
< 1000 μg (2 ampoules)	32 (74%)	4 (10%)*
< 1500 μg (3 ampoules)	39 (91%)	12 (29%)*

* $P < 0{\cdot}0001$.

needed with the conventional treatment (Table 2). In the experimental group 32 women (74%) were delivered after only 1 or 2 ampoules of the drug, compared with only four women (9·5%) in the conventional group ($P<0{\cdot}0001$, Table 2).

All 85 women were delivered vaginally within 72 h from the start of the induction. Only two women, one in each group, had an induction-to-delivery interval >36 h. Half the women in each group were delivered within 12 h. By chance there were more nulliparae in the experimental than in the conventional group (not statistically significant), which could be expected to result in longer induction-to-delivery intervals in the experimental group. This was not the case and there were no differences in induction-to-delivery intervals between the two treatment groups (Table 3). Complete expulsion of the placenta, obviating the need for either manual removal of the placenta or manual exploration of the uterine cavity, occurred with the same frequency in both groups (Table 3).

The overall frequency of side-effects in the experimental group was half that seen in the conventional group (21 *vs* 43%; $P<0{\cdot}05$; Table 3). These side-effects were not troublesome in either group. Nevertheless, both vomiting and diarrhoea were statistically significantly less frequent with the lower dose regimen, and pyrexia occurred less often but this difference was not statistically significant (Fig.1). Superficial venous dilatation occurred in three women in the experimental group and in one in the conventional group. This vasodilatory response was always painless and without further consequences. Fewer women in the experimental group received analgesia than in the conventional group, but the difference was not statistically significant (Table 3).

Various biochemical and haematological variables were determined before and after induction. None of these, including white cell counts, haemoglobin and haematocrit, showed statistically significant differences between the two groups. Complications, other than the side-effects listed in Table 3, were not encountered.

Discussion

To our knowledge this is the first reported randomized controlled comparison of different treatments to end pregnancy after fetal death. Induction of labour in these circumstances is a sensitive issue and it requires a high level of individualized care. Understandably, clinicians are not readily inclined to subject these women to formal, controlled experimentation. This is necessary, however, if care options for these women are to be improved.

The efficacy of prostaglandins in achieving delivery after antepartum fetal death now contrasts markedly with the unsatisfactory results of previous methods (Keirse & Kanhai 1989; Tindall & Reid 1989). However, delivery within a reasonable time interval has been the main focus of attention in developing appropriate methods of prostaglandin administration. Side-effects and maternal discomfort have tended to receive

Table 3. Effects of two regimens of sulprostone administration: (i) experimental (1 μg/min continuously), (ii) conventional (1500 μg in 8 h, repeated if necessary)

Effects	Experimental treatment ($n=43$)	Conventional treatment ($n=42$)
Induction–delivery interval (h)		
Median	12	12
Range	4–39	4–61
No. delivered		
Within 12 h	20 (47%)	21 (50%)
Within 24 h	39 (91%)	34 (81%)
Within 35 h	42 (98%)	41 (98%)
No. with complete expulsion of placenta	29 (67%)	26 (62%)
No. receiving analgesia		
All types	30 (70%)	36 (86%)
Epidural	7	8
No. with side-effects		
Vomiting	8	16
Diarrhoea	1	6
Pyrexia (>38°C)	2	7
At least one of the above	9 (21%)	18 (43%)*
Blood loss (ml) Median	130	100
Range	10–1400	10–1500
No. with blood loss		
>500 ml	5	3
>1000 ml	2	1

* $P < 0{\cdot}05$

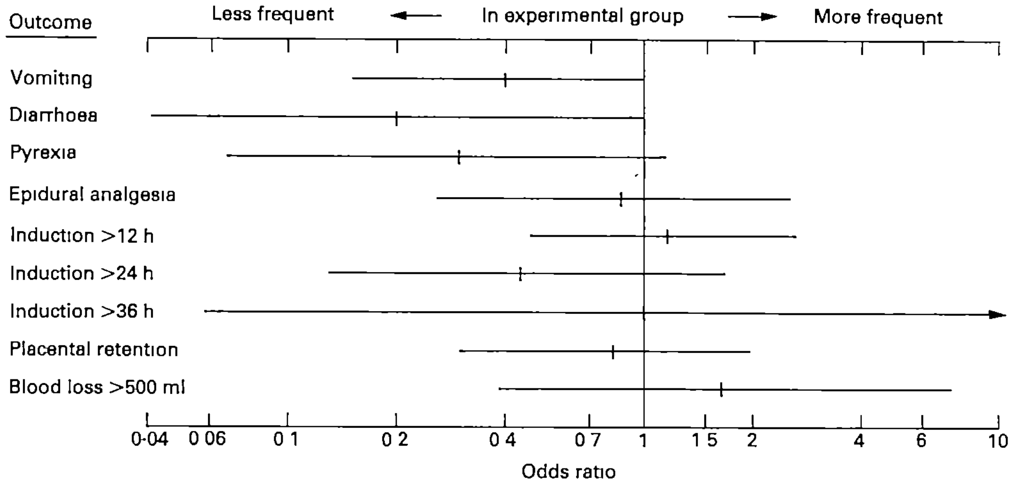

Fig. 1. Effects of the experimental (1 μg sulprostone/min continuously) *vs* conventional (1500 μg sulprostone in 8h, repeated if necessary) treatment on various outcomes (odds ratio with 95% confidence interval). Odds ratios below 1 indicate an advantage for the experimental treatment, and confidence intervals that do not cross the vertical line drawn at a ratio of 1 indicate that this advantage is statistically significant at the 5% level.

a lower priority than the overall efficacy in bringing pregnancy to an end. Large multicentre surveys, for example, have reported vomiting in >50% and diarrhoea in >40% of the women induced with different prostaglandin preparations (Southern *et al.* 1978; Wallenburg *et al.* 1980). There is thus considerable scope for developing regimens which minimize the unpleasantness for women of a labour that is destined to end with the birth of a dead baby.

Because of the rarity of antepartum fetal death, obstetricians have tended to adopt methods that had been shown to be efficacious for terminating second-trimester pregnancies (Keirse 1982). Some of these regimens are inappropriate and too few women derive benefit from the knowledge that induction of labour is more readily achieved after the fetus has died than when the fetus is alive (Luengo *et al.* 1977; Karim *et al.* 1979; Schulman *et al.* 1979; Keirse 1982; Ratnam & Prasad 1986).

Multicentre randomized controlled trials appear to be the only satisfactory way of assessing the relative merits of alternative regimens. Our study has shown that such trials are feasible and that they can provide answers that are clinically useful. Thus, the lower infusion rate was demonstrated to result in 50% fewer gastrointestinal side-effects than observed with the conventional treatment. This was achieved without increasing the induction-to-delivery interval and with a large reduction in the amount and cost of the prostaglandin used.

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Survey of attitudes to testing for human immunodeficiency virus infection in antenatal clinics in West Glamorgan

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Summary. A total of 1023 women attending hospital antenatal clinics in West Glamorgan was surveyed by means of a self-administered questionnaire, to determine their attitudes to HIV testing in pregnancy. The response rate was 98%. Of the responders, 94% had no objection to their antenatal blood specimen being tested for HIV infection. Of the non-objectors, 55% wished their permission to be asked first, and 92% wished to be informed of the result, i.e. they wished for named testing. With regard to knowledge of other tests for infectious diseases performed on antenatal blood specimens, only 1·5% had totally correct knowledge, and only one in three knew that their blood was tested for syphilis. The implications of anonymous and named HIV testing are discussed, together with estimates of prevalence of HIV infection in women attending antental clinics, the rate of vertical transmission, and the prognosis for an infected baby.

The District Maternity Services Liaison Committee in West Glamorgan met in October 1988 and considered the recommendations of the Smith Working Group on the Monitoring and Surveillance of HIV infection and AIDS (Smith Report 1988), in particular as they related to pregnant women.

Although multidisciplinary, their views were clear and in accord:

(1) That it was desirable to provide baseline information on the prevalence of HIV infection in the general population, and that voluntary named testing might be possible within selected antenatal clinics as proposed by the Report, with the opportunity for refusers to be tested on an un-named basis.

(2) That the Division of Obstetrics would support the introduction of testing of all antenatal patients, preferably named if counselling services were made available, or anonymously.

(3) That pregnant women would agree to and accept named testing if it was introduced routinely at all antenatal clinics, a view strongly expressed by the lay members of the Committee.

This was in marked contrast to the statement on the ethical considerations of HIV infection and AIDS produced by the General Medical Council in May 1988 which recommended that pregnant women should not be singled out because they are a vulnerable group who should not be subjected to 'unnecessary additional stress'. The Council argued that pregnant women may believe that if they refuse a voluntary HIV test, the rest of their care could be prejudiced, and the

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validity of their consent may be open to question.

Various professionals, and both the British Medical Association and the Faculty of Community Medicine, urged the adoption of anonymous testing of blood from patients who had voluntarily given it for other tests, but who had not specifically consented to an HIV test, as being the best way to produce population prevalence information, without the potential bias of refusals of voluntary testing by those most at risk of being HIV positive, and the expensive problem of checking for false positives. This was the advice accepted by the Government when it announced new steps to monitor the spread of HIV infection in a press release from the Department of Health on 23 November 1988.

The West Glamorgan District Maternity Services Liaison Committee decided to test the validity of its own perceptions by undertaking a survey of women attending the three main hospital antenatal clinics, by means of a simple self-administered questionnaire distributed by midwives to women attending first booking clinics. The opportunity was also taken to test the knowledge of pregnant women of the infectious diseases for which their antenatal blood specimens are tested, as specific consent for each test is not sought, even though this is named testing and the blood sample is the patient's property.

Subjects and methods

Questionnaires were given to 1023 women attending antenatal booking clinics in West Glamorgan over a period of 4 months; 22 women refused to complete them, giving a response rate of 97·8%. The questionnaire was confined to one page and the wording was simple, as follows:

(1) Is your age between (tick one only)
15 and 19 years ____
20 and 29 years ____
30 and 39 years ____
40 and 49 years ____

(2) Which, if any, of the following infections do you think your blood is tested for at present in antenatal clinics?
Tuberculosis ________
German measles (Rubella) _______
Syphilis ________
Infective hepatitis (jaundice) ________
Gonorrhoea __________
Malaria __________
Toxoplasmosis __________
Mumps __________

(3) Would you object to your blood being tested for AIDS (HIV infection)?
YES [ ] NO [ ]
If 'No' please answer the following two questions.

(4) Would you wish to be asked for your permission before your blood was tested for AIDS?
YES [ ] NO [ ]

(5) Would you wish to be told the results of an 'AIDS' test?
YES [ ] NO [ ]

Any comments ....
....

Results

The analyses relate to the 1001 responders.

Attitudes to AIDS testing

Overall, 940 (94%) of the responders had no objection to their blood being tested for AIDS (HIV infection). Table 1 relates to these 940 and cross-tabulates their answers to questions 4 and 5.

Table 1 shows that the organization of testing, in order of acceptability, was as follows. (i) Named voluntary testing (wishing permission to be asked and wishing to know result) 53%. (ii) Named universal testing (not wishing permission to be asked and wishing to know result) 39%. (iii) Anonymous testing (not wishing to know result) 5%. The remaining 3% were not known.

Most of the women who did not object to testing stated that they wished to be informed of the result, 868 (92%), and this was not significantly different in the age groups, ranging from 92% in the youngest group, to 94% of those aged 20–29, to 97% of those aged ≥ 30 ($0{\cdot}10 > P > 0{\cdot}05$).

Knowledge of tests

A subsidiary aim of the survey was to determine the knowledge that pregnant women have of the infectious diseases for which blood specimens taken in antenatal clinics are already tested. In a list of eight diseases, respondents were asked to tick any for which they believed tests were performed on their antenatal blood specimens, and the results are listed in Table 2.

A surprisingly low 1·5% had totally correct

Table 1. Frequency distribution of pregnant women who did not object to HIV testing, with regard to wish to have their permission asked and wish to be informed of result.

Wish to be informed of result	Wish permission to be asked			
	Yes	No	NK	Row total
Yes	496	363	9	868
No	22	25	2	49
NK	1		22	23
Column total	519	388	33	940

NK, Not known.

knowledge that their blood was tested for syphilis, rubella and toxoplasmosis only, while another 9·2% knew of these three diseases, but also thought that a variety of other diseases were tested for.

One in five thought incorrectly that their blood was tested for gonorrhoea, while only one in three knew that their blood was tested for syphilis.

Overall, 98 (approximately 1 in 10) women responded to the invitation to make additional comments, five of whom were objectors to testing and 93 non-objectors. Points made could be classified as 'supportive of testing', 'concern over test' and 'education and counselling'.

Those comments supportive of testing wanted to detect HIV positives not only in pregnant women but in the population as a whole; to detect infected babies, with concern over the health of the baby, and wishing the option of abortion; and to protect staff.

The concern over the test related to its effects on insurance and mortgages, and the implications for family members.

More education and counselling were requested for children, for antenatal patients, and also for antenatal patients with regard to other tests performed.

Discussion

The main purpose of the survey was to test the validity of the views of the District Maternity Services Liaison Committee that named testing would be acceptable to women attending antenatal clinics, either universally or by voluntary opt-in; and that their second choice of anonymous testing would also be acceptable to women.

The results support the Committee's views in that 94% of the responders had no objection to testing, with 92% of those who did not object wishing to be informed of the result, i.e. wanting named testing. Most of the women who approved named testing preferred it to be on a voluntary basis, i.e. their permission to be asked before testing.

It is of note that only one woman in three knew that her blood was tested for syphilis, and even though syphilis has some of the public health and ethical implications of HIV testing, specific permission is not sought from each woman for this named testing.

The Report of the RCOG subcommittee (1987) stated that 'The DHSS recommendation that information on the nature and specific implications of all tests performed in pregnancy should be given to the woman concerned should apply no less to HIV testing'. And further after being given the appropriate explanation and information as for any other test in pregnancy, being given the option to refuse.

The survey results indicate that either women are not listening to the information given, or that antenatal care is so standardized and routine, and so accepted by women as being in their best interests, that explanations are thought unnecessary.

Implications of testing

There would be no additional costs of venepuncture, as tests for HIV antibodies would be made on antenatal blood samples taken for other purposes. However, there are additional cost impli-

Table 2. Knowledge of tests for infectious diseases performed on antenatal blood specimens.

Disease	Women who thought test was performed	
	Number	Per cent of responders
Tuberculosis	223	22·3
Rubella*	846	84·5
Syphilis*	353	35·3
Infective hepatitis	337	33·7
Gonorrhoea	189	18·9
Malaria	24	2·4
Toxoplasmosis*	242	24·2
Mumps	74	7·4

*Tests actually performed.

cations of named (compared with anonymous) testing, including the greater volume of initial tests (all women attending antenatal clinics rather than a sample); confirmatory tests necessary to eliminate false positives; costs of follow-up of true positives; costs of contact tracing; costs of introducing obstetric counselling services; and costs of abortions requested (discounted by costs of caring for an infected baby).

Non-financial costs of named testing relate to the legal implications with regard to jobs, mortgages and insurance, and effects on family and wider relationships.

Anonymous testing, while providing more reliable prevalence data than are available at present, as a basis on which to plan services and facilities, also has costs. These include the loss of options for the infected women; the loss of contact tracing; the loss of the chance to counsel and support the woman and monitor her in subsequent pregnancies; the loss of follow-up of the infected child, and the child not infected but likely to have a sick or dying mother; and the fact that anonymous testing can have no direct impact on the spread of the AIDS epidemic.

The announcement on 23 November 1988 by Mr Kenneth Clarke, that he was asking the Medical Research Council to bring forward proposals for a programme of anonymous screening, was accompanied by the statement that the Government is to go ahead with AIDS screening of pregnant women in Scotland on a named voluntary basis, with two studies already announced in Dundee and Edinburgh.

A district such as West Glamorgan could offer to act on the results of this survey and introduce named voluntary testing of women in antenatal clinics, with a reasonable expectation of success. Before doing so there would be a need to estimate the consequences based on available studies, until the results of longer follow-up studies give more precise risk data relating to the number of infected women likely to attend antenatal clinics, the rate of vertical transmission of infection from mother to baby and the amount of counselling required.

Estimates of the prevalence of HIV infection in the heterosexual population are given variously by the blood donor screening programme and the GUM Clinic Survey (Smith Report 1988), and by surveys among childbearing women in Massachusetts (Hoff *et al.* 1988) and those attending antenatal clinics in New York (Landesman *et al.* 1987) and in City and Hackney Health Authority (Heath *et al.* 1988).

The prevalence in West Glamorgan may be lower than in London, but if the latter estimate of 0·3% is applied to the 5500 annual births in West Glamorgan, possibly 16 women attending antenatal clinics in a year could be seropositive. However, as 40% of HIV-seropositive women known to the UK Communicable Disease Surveillance Centre up to the end of 1988 were intravenous drug users, as well as 20% of women with known AIDS, a knowledge of the extent of intravenous drug use amongst women in West Glamorgan may serve to modify this estimate.

An estimate of the risk of transmission of HIV infection from mother to child is obtained from the European Collaborative Study (1988) and the Italian Multicentre Study (1988). If the lower estimate of the former, 24%, is applied to the possible 16 seropositive women attending antenatal clinics in West Glamorgan, four babies could be born with HIV infection, of whom one might develop AIDS in the first year of life. The other three antibody-positive babies would need to be followed up as, even though clinically well, it could not be assumed they would escape infection.

Counselling services

The advice needed by a woman who is discovered to be HIV positive in early pregnancy relates to the effect of continuation of the pregnancy on her progression to clinical disease; the risk of infection of her unborn child; and the prognosis for her child if infected. There may be an additional need for counselling in relation to drugs misuse in some women.

There is conflicting evidence about the effect on the mother's health (Scott *et al.* 1985; Minkoff *et al.* 1987; MacCallum *et al.* 1987; Johnstone *et al.* 1988). The risk of transmission of infection to the unborn child could be given as 1 in 4, but firmer evidence is needed on how this risk varies with the mother's stage of HIV infection. Data from the European Collaborative Study (1988) showed that maternal health during pregnancy may be important in predicting outcome for the infant, since infants born to mothers who had symptoms during pregnancy were nine times more likely to develop AIDS or AIDS-related complex, compared with those whose mothers were clinically well.

Such surveys allow estimates of risks to be formulated, but there are also data on the known volume of children infected by vertical transmission, for both the USA and the UK. The US Centres for Disease Control, Aids weekly surveillance report on 12 September 1988 attributed 902 out of a total of 72 766 cases of AIDS to vertical transmission from mother to child, i.e. 1·2% of total cases. The UK Communicable Disease Surveillance Centre (CDSC) Report on 31 May 1989, attributed 21 out of a total of 2296 cases of AIDS to 'Child of at risk/infected parent', i.e. about 1% of total cases. It is of note that these percentages are similar in both countries, perhaps because they represent data collected on a wide geographical basis, thus cancelling out pockets of high and low incidence which might affect results in local studies.

The UK CDSC report to the end of 1988 on the prevalence of HIV seropositives attributes 35 out of a total of 8025 to 'Child of at risk/infected parent', i.e. 0·44%. Relating 0·44% of HIV seropositives to 1% of AIDS cases might imply that only half of the vertical transmission HIV seropositives are known, or that there is a greater volume of or more rapid progression to clinical AIDS in children infected perinatally. Babies of all seropositive women would need to be included in the British Paediatric Surveillance Scheme, which is aimed at establishing the risks and consequences of infection in children.

Conclusion

The Report of the RCOG Subcommittee (1987) stated that the risk of transmission of HIV infection to clinicians and midwives must be avoided, because this infection is unique in that there is no prophylactic vaccine, no curative treatment, and infection is followed by high long-term morbidity and mortality.

For the same reasons, this avoidance of risk also applies to the rest of the population, but the choice of anonymous testing is based on the argument that there is no need to invade individual privacy and define each infected person, because measures to control infection are advised which will be successful in preventing spread if applied to all people, and all pregnancies. It seems self-evident that greater care would be taken in the knowledge of the reality of HIV infection rather than of the probability, and perhaps the willingness of women attending antenatal clinics in West Glamorgan to participate in named testing reflects this. In considering this choice, the Health Authority must decide on the balance between the service and other costs and the public health gains, in this section of the population where the prevalence of HIV seropositives is low, and has concluded that such a service should not be introduced until the prevalence of infection is higher, and both the rate of vertical transmission and the prognosis for mother and baby are known with greater certainty, enabling effective counselling services to be introduced.

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The efficacy of paracervical injections of lignocaine before laser ablation of the cervical transformation zone. A randomized placebo-controlled double-blind clinical trial

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Summary. In a prospective double-blind randomized placebo-controlled clinical trial the efficacy of paracervical lignocaine was compared with saline in reducing pain in 70 women undergoing laser ablation of the cervical transformation zone. Paracervical lignocaine had no significant measurable effect on reducing the pain experience during the laser procedure. The mean subjective visual linear analogue pain score in the lignocaine and saline groups was 27% (95% CI 17 to 38) and 30% (95% CI 24 to 41) respectively ($t = 1·0$; $P = 0·35$). The median (quartiles) objective pain scores for the same groups were 0 (0–2) and 0 (0–1) respectively ($P = 0·58$).

Conduction anaesthesia of the cervix by paracervical injection of lignocaine is a well-described technique (Baskett & Carson 1974). It is used at cervical dilatation during termination of pregnancy (Strausz & Schulman 1971), IUCD insertion (Littlepage *et al.* 1969) and laser ablation of cervical dysplastic lesions (Lowles *et al.* 1983). Individual variations in the perception of and response to pain are large and it is easy to see how a clinician can adopt a technique that should intuitively reduce iatrogenic pain without formally assessing it. As the efficacy of paracervical lignocaine before laser surgery has not been reported (Anon 1989) we performed a randomized double-blind clinical trial.

Subjects and methods

The study included 70 women with a new colposcopic and histological diagnosis of a cervical dysplastic lesion suitable for laser ablation. Each woman had had one colposcopic examination and had received a preliminary explanation of laser treatment. The following prospective exclusion criteria were used: previous cervical surgery, more than one colposcopic examination, menopausal or perimenopausal status, sensitivity to lignocaine, patient refusing paracervical injection or refusing to be recruited into the trial, or vaginal involvement of the lesion. At the laser clinic, details of anxieties score (linear analogue and HAD scores; Zigmond & Snaith 1983), depression scores (HAD score), linear analogue dysmenorrhoea scores, premenstrual syndrome scores, parity and last menstrual period were recorded. A further explanation of laser treatment and its implications was offered together with positive reassurance that the procedure would be bearable. Consenting patients were then randomized to receive either 2% lignocaine or normal saline from a numbered vial. Each vial could only be identified at the end of the study by its number which was allocated prospectively according to a block randomized code. A bilateral paracervical block was delivered as described by Littlepage *et al.* (1969)

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Table 1. Effect of paracervical lignocaine on pain experience during laser ablation of the cervical transformation zone

Pain scores	Paracervical lignocaine ($n = 35$)	Paracervical saline ($n = 35$)
Visual analogue pain score		
Mean (95% CI)	27% (17 to 38)	30% (24 to 41)
Objective pain score		
Median	0	0
Quartiles	0–2	0–1
Mean	1·6	1·1

by injecting a total of 10 ml into the paracervical tissues. A guarded pudendal block needle (Rocket of London) was used to ensure a constant depth of injection (10 mm). The women were then returned to the waiting room for 10–30 min. Laser ablation of the entire transformation zone to a depth of approximately 7 mm was performed with a continuous fine beam (spot size 1·5 mm) 35-W CO_2 laser by a separate surgeon in a second suite. Pain was objectively scored by the attending nurse who assessed the woman's level of vocalization (2 = moan/cry; 1 = gasp; 0 = no vocalization), muscle tension of the upper limbs (2 = the clenching the bed etc.; 1 = making a fist; 0 = relaxed), thigh movements (2 = adduction; 1 = twitchy; 0 = relaxed). The laser operator independently scored movements of the thigh as well as perineal movement (2 = bottom movement up the bed; 1 = speculum twitches; 0 = no movement/relaxed). The size of the transformation zone and blood loss were recorded. At the end of the procedure and after a further explanation, the women scored their pain on a 120-mm visual linear analogue scale.

Statistical analysis

Objective pain scores were represented by the sum of the scores of vocalization, muscle tension of the upper and lower limbs and perineal movement (range 0–8). The severity of pre-menstrual symptoms was assessed by adding the number scores awarded for premenstrual tension, bloatedness, headache, irritability, tiredness, depression, breast and finger swelling.

Before the trial, data were collected from 20 women in order to estimate the expected standard deviation for the pain scores. The necessary sample size was then calculated to determine a 30% improvement in subjective pain, assuming a power of 80% and an alpha error of 5%.

Linear analogue scores were analysed by non-paired Student's *t*-test. Objective pain scores, anxiety and depression HAD scores, premenstrual syndrome scores, parity, phase of the menstrual cycle, the size of the transformation zone and blood loss were analysed by Mann–Whitney testing.

Results

There was no statistically significant difference in the pain experienced between the group receiving paracervical lignocaine and the group receiving saline. The women in the saline group appeared slightly more comfortable than those in the lignocaine group. The median objective pain score was 0 (mean 1·6) in the lignocaine group and 0 (mean 1·1) in the saline group ($P = 0·58$). However, the women in the saline group rated the procedure as slightly more painful compared with those in the lignocaine group. The pain score was 27% for lignocaine and 30% for saline ($t = 0·98$; $P = 0·35$) (Table 1). These differences were small and not statistically significant. The colposcopic surgeon and the attending nurse agreed independently on the score for thigh movements in all but one woman.

Two women, one from each group, required supplementary analgesia (intravenous fentanyl) and their discomfort was reflected by their pain scores. The two groups were comparable in terms of anxiety states, parity, dysmenorrhoea scores, and premenstrual tension scores. The respective mean values for those in the lignocaine and saline groups were 64% and 61% for the anxiety visual linear analogue score; 8·5 and 9·0 for the anxiety HAD score (maximum 18); 3·3 and 3·4 for the depression HAD score (maximum 18); 2·5 and 2·6 for the premenstrual syndrome scores (maximum 9); 1·4 and 1·2 for the size of the transformation zone (maximum 2) and 0·25 and 0·40 for the estimated blood loss (maximum 2). In the lignocaine group 37% were nulliparous compared with 32% in the saline group, and 47% used oral contraceptives compared with 53% in the saline group.

Discussion

Some of the perceived pain due to laser ablation of the cervical transformation zone may be due to local heat generation. If the temperature rise directly affects the small C nerve fibres responsible for carrying pain impulses, the discomfort will be experienced by the patient as a sharp and well-localized pain. However, most patients experience a dull ache similar to dysmenorrhoea which is poorly localized to the lower abdomen or pelvis. This sensation may be due to prostaglandin release and the initiation of uterine contractions. This humoral response will be unaffected by paracervical conduction anaesthesia.

In our patients, paracervical injection of an anaesthetic agent does not decrease the pain experienced during laser ablation to a measurable degree. Supporters of paracervical blocks may question our administration of the anaesthetic or the way we measured pain. However, visual linear analogue pain scores are thought to be the best way of representing the patient's experience of discomfort and are more accurate than other techniques such as verbal descriptive rates (Huskisson 1983). Our anaesthetic technique is similar to the popular method used by Iversen (1985), Strausz & Schulman (1971), Littlepage *et al.* (1969), Goodlin *et al.* (1976), Rotchell (1976), Lowles *et al.* (1983) and Lewis *et al.* (1971) and was administered by an experienced colposcopist. We allowed a minimum of 10 min to elapse before starting therapy thus ensuring that the nerve block had time to work, and by limiting the injection–treatment interval to only 30 min, we did not allow the paracervical block time to wear off (Covino 1984). Supporters of the paracervical block may further argue that lignocaine does reduce subjective pain but our sample size was too small to reject the null hypothesis to any degree of statistical significance. If the difference in linear analogue pain scores were real we would need to recruit a further 10 000 patients to detect a statistically significant difference but the probability that paracervical lignocaine makes a 15% difference to a patient's pain score is less than 1% (i.e. the probability of a type II error <1%).

Paracervical injections with local anaesthetic agents are uncomfortable, occasionally painful and induce dizziness and light-headedness in many patients. Moreover, they can induce bradycardia (Goodlin *et al.* 1976) and the rare patient can be sensitive to lignocaine. Direct injection of small amounts (2 ml) of local anaesthetic combined with a vasoconstrictor may be of benefit to patients in the colposcopy laser clinic (Lee *et al.* 1986) but paracervical lignocaine offers no significant advantage.

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Monozygotic twin pregnancy: diagnostic and Doppler ultrasound studies

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Summary. Of 178 consecutive twin pregnancies, 63 were both monozygotic and also studied prenatally by real-time B-scan (and usually Doppler) ultrasound. The 48 pregnancies with monochorionic placentas (in which vascular anastomoses are almost universal) were compared with the 15 monozygotic pregnancies having dichorionic placentas. The type of placenta found at delivery was predicted with substantial accuracy by ultrasound examination in mid-pregnancy. We were unable to identify any inter-group difference in fetal growth rate, discordance of fetal growth between twins or pattern of umbilical artery flow velocity waveform. In the absence of the rare florid twin transfusion syndrome, the vascular anastomoses that have been shown to be common in monochorionic placentas do not exert a strong influence on fetal growth or fetoplacental blood flow.

There is a high rate of fetal loss from twin pregnancies generally (Patel *et al.* 1984) and from monozygotic pregnancies particularly (Naeye *et al.* 1978). Preterm labour and fetal growth retardation are commonly associated with both types of twinning, and monozygotic pregnancies are thought to be at increased disadvantage because of more frequent fetal malformation (Fogel *et al.* 1965) and the adverse consequences of monochorionic placentation. Three-quarters of monozygotic pregnancies have monochorionic placentas and, almost always, these contain vascular anastomoses connecting the circulations of each twin (Robertson & Neer 1983). Arteriovenous anastomoses enable the shunting of blood from one fetus to the other and thus the twin transfusion syndrome. In its most florid form this is associated with anaemia and growth retardation in the donor twin and polycythaemia in the recipient, and with oligohydramnios in the amniotic sac of the donor and polyhydramnios in that of the recipient (Benirschke & Kim 1973); fetal ascites may occur. These features, which are rare, may be identified on ultrasound examination (Wittmann *et al.* 1981) to allow the possibility of treatment (Wittmann *et al.* 1986) to try to avoid early delivery.

The exact pathophysiological significance of vascular anastomoses in monochorionic placentas in the absence of florid twin transfusion syndrome is not known. Anastomoses may be associated with differences between twins in haemoglobin concentration and birthweight during the third trimester (Rausen *et al.* 1965) and with a spectrum of pathology including fetal growth retardation. To investigate the significance of such anastomoses we have studied monozygotic twin pregnancies and compared those with monochorionic placentas (in which vascular anastomoses are almost universal) with

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Table 1. Characteristics of study groups

	Monozygotic monochorionic	Monozygotic dichorionic
Number of pregnancies	48	15
Birthweight (kg)		
Twin 1	2.33 (0·62)	2·39 (0·52)
Twin 2	2·28 (0·64)	2·39 (0·52)
Difference	0·25 (0·21)	0·27 (0·25)
Gestation at delivery (weeks)	35·6 (3·5)	35·7 (2·8)
Both twins SGA	6 (13%)	0
One twin SGA	7 (16%)	4 (27%)
Preterm delivery	18 (38%)	6 (40%)
Stillbirths	3/96 (3%)	0
Neonatal deaths	4/96 (4%)	0

Results are shown as mean (SD) or *n*(%) as appropriate.
SGA, Small-for-gestational-age.

those having dichorionic placentas (in which anastomoses are so extremely rare that their possibility can be disregarded for practical purposes) (Robertson & Neer 1983). We have investigated, with ultrasound, whether the type of placentation can be accurately determined prenatally and whether discordant patterns of fetal growth are more likely in association with monochorionic placentation. We have also investigated whether such placentas are associated with concordant patterns of umbilical artery blood flow as determined by Doppler ultrasound.

Subjects and methods

Between August 1984 and December 1987 we investigated 178 consecutive twin pregnancies of >12 weeks gestation delivered in our unit. Of these, 159 were studied prenatally with ultrasound, the remainder having been transferred from other units because of complications (usually established or spurious preterm labour). Ultrasound examination by real-time sector scanner usually comprised detailed inspection of fetal anatomy and confirmation of gestational age by fetal measurement at around 17 weeks (following initial diagnosis at routine ultrasonography at the first clinic visit). Subsequent measurements of the abdominal circumference and area of both twin fetuses and (latterly) Doppler study of umbilical artery flow velocity waveforms were performed at 4-weekly intervals. Fetal measurements were obtained with a sector scanner and the mean of at least two circumference (and area) values was used. This equipment was also used to identify the umbilical cord of each twin and thus to guide the direction of the Doppler ultrasound probe (4 MHz continuous wave). The umbilical artery waveforms were recognized by their characteristic shape, recorded during fetal apnoea and analysed over 1·6 s to average the values from three or four waveforms. The AB ratio (Stuart *et al.* 1980) was calculated. When there were absent end-diastolic velocities an arbitrary value of 9 was given for the AB ratio.

Of the 159 pregnancies, zygosity was established after delivery in 142 (89%) by inspection of the placenta (monochorionicity indicating monozygosity), sex of the babies (discordant sex indicating dizygosity) or, when necessary, by analysis of red cell antigens of the ABO, Rhesus, MNS, Kell, Duffy, Kidd, Lutheran and Wright systems (Wilson 1970). In all 17 pregnancies in which zygosity was not established, the placenta was dichorionic and the babies of like sex; in three there had been longstanding intrauterine death of one twin which pre-empted blood group studies while in the others blood was not submitted for testing. Of the 63 monozygotic pregnancies, 48 had monochorionic and 15 had dichorionic placentas. These constitute the study groups and their characteristics are shown in Table 1.

There were seven perinatal deaths in monozygotic twins, all from the monochorionic group. One baby was stillborn at 31 weeks because of placental abruption; the co-twin survived. Another baby was stillborn at 34 weeks following intrapartum asphyxia when dystocia from massive fetal ascites complicated delivery; ascites had not been present at previous ultrasound examinations, the last being 3 weeks before delivery. The third stillbirth was of a 480 g

Table 2. Prediction of type of placentation by ultrasound inspection for the dividing membrane in 42 pregnancies at 17 weeks

	Placenta	
Ultrasound finding	Monochorionic	Dichorionic
Dividing membrane		
Easily seen	7	11
Faint	18	0
Not seen	6	0

fetus papyraceous whose death during the second trimester had been noted but which was born at 29 weeks. The latter two pregnancies have not been included in analyses of size or weight. Four neonatal deaths resulted from the immaturity of two pairs of twins born at 23 and 26 weeks.

There were no babies with major malformations.

Results

In 42 pregnancies the dividing membranes were investigated by ultrasound at 17 weeks; the usefulness of the ultrasound findings for the prediction of the type of placenta is shown in Table 2. In those pregnancies in which no dividing membrane could be seen, the placenta was always monochorionic/diamniotic; there were no monochorionic/monoamniotic placentas in this series.

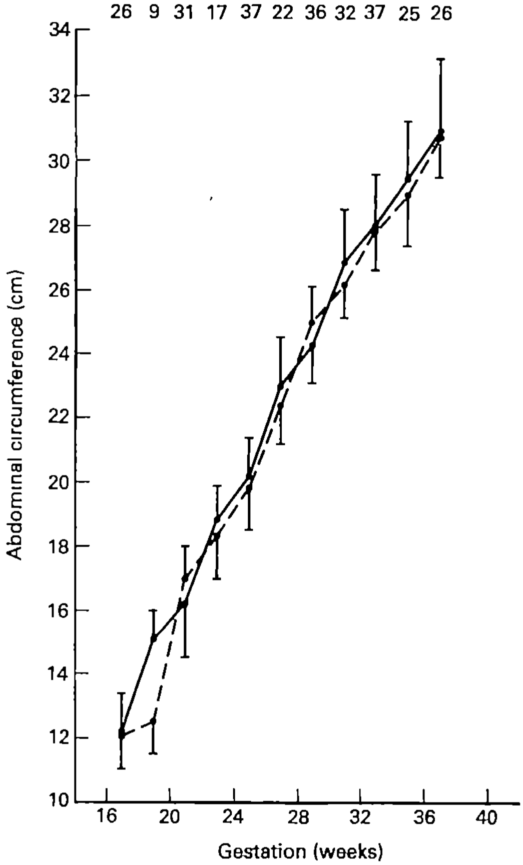

Fig. 1. Abdominal circumference measurement of leading twin fetuses (mean ± 1SD) from monochorionic pregnancies (———) and dichorionic pregnancies (——). The total number of measurements analysed in each 2-weekly block is shown at the top.

There was no consistent or significant difference in abdominal circumference (or area) measurements of either the leading twin (Fig. 1) or the second twin between monochorionic and dichorionic pregnancies (Table 3). Within-pair differences in abdominal circumference were calculated by subtracting the value of the second twin from that of the first; all values were regarded as having a positive sign. There was no consistent within-pair difference in abdominal circumference between the two groups (Table 4).

There are fewer data from the Doppler ultrasound study which was restricted to 32 pregnancies in the latter part of the series (22 monochorionic, 10 dichorionic). The results have been analysed in 4-weekly blocks to ensure both sufficient numbers of results and also that no more than one pair of results per pregnancy is included in any block. Comparisons of AB ratios of leading and second twin fetuses are shown in Table 5 and within-pair differences in AB ratios are shown in Table 6. The results show the normal fall in the AB ratio as pregnancy advances. There were no consistent differences in the AB ratios from the two types of monozygotic pregnancy (Table 5). A significant difference (at the 5% level) in within-pair differences in the AB ratio at 28–31 weeks was not found when the data were reanalysed after excluding pregnancies in which one or both fetuses showed absent end-diastolic velocities in the umbilical artery waveform (and therefore was given an arbitrary AB ratio value of 9).

Discussion

The pregnancies which we studied were established to be monozygotic either because the placenta was monochorionic or because of sex and blood group concordance in association with a dichorionic placenta; these latter criteria have only a 3% chance of misclassifying a dizygotic pregnancy as monozygotic (Wilson 1970). There was greater perinatal loss from the monochorionic monozygotic pregnancies (72·9/1000) than from the dichorionic monozygotic pregnancies (none). Such comparisons have the potential to exaggerate the relative rate of loss from monochorionic pregnancies because if one of twins of like sex is stillborn (thus pre-empting blood

Table 3. Comparison of abdominal circumference (AC) measurements of leading twin fetuses (twin 1) and of second twin fetuses (twin 2) of monozygotic monochorionic (MZMC) and monozygotic dichorionic (MZDC) pregnancies

	AC (twin 1)				AC (twin 2)			
	MZMC		MZDC		MZMC		MZDC	
Gestation (weeks)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
16–17	20	120·5 (10·1)	6	121·8 (13·8)	20	118·7 (9·1)	6	118·8 (10·8)
18–19	6	151·6 (9·1)*	3	126·9 (10·4)*	6	149·7 (13·7)	3	130·2 (11·7)
20–21	23	162·6 (17·5)	8	165·9 (17·1)	23	161·6 (19·1)	8	164·5 (17·0)
22–23	11	187·5 (10·0)	6	186·0 (16·2)	11	186·4 (9·1)	6	187·0 (12·5)
24–25	28	202·9 (12·7)	9	198·1 (13·2)	23	201·0 (14·3)	9	203·2 (15·8)
26–27	14	232·0 (13·9)	8	221·5 (10·6)	14	226·9 (16·9)	8	219·3 (9·0)
28–29	26	243·3 (11·3)	10	244·6 (14·6)	25	240·4 (15·0)	10	248·4 (20·5)
30–31	24	268·7 (16·1)	8	262·5 (11·6)	24	264·4 (22·6)	8	267·6 (20·5)
32–33	28	279·0 (16·6)	9	278·7 (15·0)	28	273·6 (21·1)	9	283·3 (19·1)
34–35	18	295·2 (14·0)	7	291·2 (16·9)	19	295·0 (25·2)	7	298·9 (17·4)
36–37	19	311·6 (20·0)	7	311·2 (15·9)	19	309·3 (21·1)	6	306·6 (42·2)

*$P<0{\cdot}05$, analysis by Student's *t*-test

group studies) zygosity will only be established if the placenta is monochorionic. This source of bias is not relevant to neonatal deaths. We found both stillbirths and neonatal deaths to be more common in the monochorionic group. The causes of death seemed diverse and, although none could be directly attributed to classical twin transfusion syndrome (including the case of fetal ascites), we cannot disprove the possibility that vascular anastomoses contributed to these losses.

The type of placentation found at delivery was predicted with substantial, though not complete, accuracy by ultrasonographic inspection for a dividing membrane in mid-pregnancy; when this was faint or not seen, the placenta was always monochorionic. This is consistent with the findings of others (Barss *et al.* 1985) and may be useful information to assist management of discordant malformation (when 'selective feticide' is considered), suspected twin transfusion syndrome, or intrauterine death of one twin in late pregnancy. Selective feticide by injection into the circulation of the affected fetus will pose a hazard to the co-twin if vascular anastomoses are present. Similarly, there may be a risk of disseminated intravascular coagulation, with consequent renal and brain damage, in a surviving twin by the passage of thromboplastins from a shared placenta after the other fetus has died (Hanna & Hill 1984).

Chronic twin transfusion syndrome is typified by growth retardation of the donor fetus (Tan *et al.* 1979). We found little evidence of increased risk of growth retardation when the placenta was monochorionic. Although there were six monochorionic pregnancies and no dichorionic pregnancies in which both babies were small-for-dates at birth, the number of pregnancies in which one or both babies were small-for-dates was identical in both groups. Likewise,

Table 4. Within-pair differences in adbominal circumference (AC) measurements: comparisons of monozygotic monochorionic (MZMC) and monozygotic dichorionic (MZDC) pregnancies

	AC: within-pair difference			
	MZMC		MZDC	
Gestation (weeks)	*n*	Mean (SD)	*n*	Mean (SD)
16–17	20	6·6 (8·6)	6	5·9 (4·7)
18–19	6	6·1 (3·0)	3	3·3 (3·0)
20–21	23	8·1 (4·4)*	8	4·0 (4·2)*
22–23	11	6·0 (4·0)	6	7·1 (8·9)
24–25	28	8·0 (5·5)	9	7·9 (5·7)
26–27	14	8·4 (8·0)	8	4·4 (3·1)
28–29	26	12·8 (9·5)	10	7·4 (7·8)
30–31	24	15·4 (14·0)	8	10·0 (7·8)
32–33	28	16·5 (10·9)	9	12·5 (8·7)
34–35	18	14·2 (12·9)	7	13·2 (7·5)
36–37	19	14·7 (13·4)	6	23·3 (17·8)

*$P<0{\cdot}05$, analysis by Mann–Whitney *U*-test.

Table 5. Comparison of AB ratios of umbilical artery waveforms of leading twin fetus (twin 1) and second twin fetus (twin 2) of monozygotic monochorionic (MZMC) and monozygotic dichorionic (MZDC) pregnancies

	AB ratio (twin 1)				AB ratio (twin 2)			
	MZMC		MZDC		MZMC		MZDC	
Gestation (weeks)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)
20–23	12	4·5 (1·7)	7	4·1 (0·8)	10	4·8 (2·3)	7	4·7 (2·4)
24–27	13	3·9 (0·5)	5	3·6 (0·7)	13	3·6 (0·8)	5	5·1 (2·8)
28–31	14	3·8 (1·9)	6	4·5 (2·3)	14	3·8 (1·9)	6	3·4 (0·4)
32–35	17	3·3 (1·0)	7	3·9 (2·7)	17	3·8 (2·2)	7	3·6 (0·9)
36–39	9	2·5 (0·7)	4	2·8 (0·5)	10	3·2 (2·1)	4	2·7 (0·2)

There were no significant differences between the monochorionic and dichorionic pregnancies, analysis by Mann–Whitney *U*-test.

there was no significant difference in birthweight or in the intertwin difference in birthweight. Abdominal circumference (or area) is the best single ultrasound measurement to assess fetal size (Neilson *et al.* 1980). We have been unable to show any significant difference, by this measurement, in growth or size or in the frequency of divergent growth between monochorionic and dichorionic pregnancies.

Doppler ultrasound is being investigated intensively as a means of assessing the pattern of blood flow in fetal umbilical arteries and, thus, the vascular resistance of the fetoplacental circulation (Neilson 1987). The use, as in our study, of a continuous wave system, whilst simple and inexpensive, has the disadvantage that it does not permit imaging and range gating of vessels studied as do pulsed systems. We went to considerable efforts, however, to ensure that the umbilical cord of each twin was studied separately by using diagnostic imaging to guide the Doppler probe.

Various (and conflicting) opinions have been expressed about Doppler findings in twin transfusion syndrome. Thus Farmakides *et al.* (1985) described two cases, using unspecified diagnostic criteria, in which umbilical artery waveforms of the respective twins were *discordant*. In contrast, Giles *et al.* (1985) provided evidence that discordant growth in association with *concordant* umbilical artery waveforms is highly suggestive of twin transfusion syndrome. Gerson *et al.* (1987) proposed, but did not test, the hypothesis that twin transfusion syndrome is associated with normal (and concordant) umbilical artery flow to the placenta but with discordant return flow in the umbilical veins. Erskine *et al.* (1986) describe a case in which an artery–artery anastomosis in a monochorionic placenta appeared to alter the umbilical artery flow of the smaller twin in a cyclical fashion; this was attributed to increased vascular resistance during systoles synchronous with those of the co-twin. Pretorius *et al.* (1988) found no consistent pattern in eight examples of twin transfusion syndrome.

These differing reports probably reflect both the diverse nature of anastomotic links in monochorionic placentas and also a lack of satisfactory diagnostic criteria to confirm diagnosis of the twin transfusion syndrome (Danskin & Neil-

Table 6. Within-pair differences in AB ratio of umbilical artery waveforms: comparison of monozygotic monochorionic (MZMC) and monozygotic dichorionic (MZDC) pregnancies†

	AB ratio: within-pair difference			
	MZMC		MZDC	
Gestation (weeks)	*n*	Mean (SD)	*n*	Mean (SD)
Including pregnancies with AEDV†				
20–23	10	0·6 (0·9)	7	1·3 (1·9)
24–27	13	0·6 (0·4)	5	1·9 (2·2)
28–31	14	0·3 (0·3)*	6	1·6 (2·2)*
32–35	17	1·3 (1·6)	7	1·6 (1·9)
36–39	9	0·8 (1·5)	4	0·2 (0·3)
Excluding pregnancies with AEDV†				
20–23	8	0·4 (0·3)	6	0·6 (0·4)
24–27	13	0·6 (0·4)	4	0·9 (0·6)
28–31	13	0·3 (0·3)	5	0·7 (0·4)
32–35	16	1·1 (1·1)	6	0·9 (0·6)
36–39	8	0·3 (0·3)	4	0·2 (0·3)

*$P<0{\cdot}05$, analysis by Mann–Whitney *U*-test

†Analyses have been made including or excluding pregnancies in which one or both fetuses had absent end-diastolic velocities (AEDV).

son 1989). From the data presented here, we are unable to show any consistent pattern of umbilical artery waveforms resulting from vascular anastomoses in monochorionic placentas.

In summary, vascular anastomoses in monochorionic placentas do not, in the absence of the rare florid twin transfusion syndrome, exert a strong influence on fetal growth or umbilical artery velocity waveforms. Although we found more perinatal deaths in monochorionic pregnancies, these could not necessarily be attributed to vascular anastomoses.

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Melanoma and pregnancy: a long-term follow-up

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Summary. Treatment of the pregnant woman with melanoma is contentious. With the aid of a computerized melanoma register, in which pregnancy data can be recorded, 290 women with melanoma were reviewed (249 alive and 41 dead). Overall, 23 patients were pregnant at the time of diagnosis of melanoma, and another 23 became pregnant at some time after primary treatment of a melanoma. Pregnancy appears to have no significant influence on the survival of patients with melanoma, but it is recommended that pregnancy should be avoided for the first three years following excision of a melanoma.

The management of pregnant women with a melanoma can be difficult. The literature is confusing, and reports on the behaviour of melanoma in pregnancy are often contradictory. A study of a melanoma register was therefore undertaken to try to clarify this situation by asking three questions: (1) Is there a difference between pregnant and non-pregnant women in the occurrence of melanoma at various sites? (2) Do women who develop melanoma while pregnant have a worse prognosis than non-pregnant women? (3) Does a subsequent pregnancy have any effect on the prognosis of melanoma?

Patients and methods

A melanoma register has been in use at Frenchay Hospital since the early 1950s. This was originally maintained as a card index but, in 1980, the records from 1967 onwards were transferred to a computer (Briggs *et al.* 1984) with an automatic mailing facility which has ensured a regular follow-up of all patients and easy retrieval of information. The information includes details of site and thickness of the lesions, and the date and nature of any recurrence.

The women selected for this study were between 15 and 40 years of age at the time of first presentation with a melanoma. Overall, 282 records were identified from patients with stage I disease on presentation, fully assessed thickness on histological examination and who had not been lost to follow-up. The review period ranged from 2 months to nearly 20 years. Additionally, a further eight patients were included in the analysis. In these the full thickness of the lesion was not histologically assessable, usually for technical reasons, e.g. tangential cutting, but because these cases possessed useful clinical data they were included in all analyses other than those concerned with thickness.

All patients had definitive treatment in the one reconstructive plastic surgery unit. In some instances biopsy had been performed elsewhere, but in all cases wide local excisions were performed, either as primary or secondary procedures, with split skin grafting to the defect. No prophylactic lymph node dissections were undertaken. Where possible the patients were followed up every 3 months for 2 years; then every 6 months for another 2 years and subsequently yearly. All the patients were followed-up by the relevant plastic surgical team, complemented by yearly questionnaires addressed to the patients' general practitioners.

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Table 1. Distribution of slides of melanoma in pregnant and non-pregnant women

	Head and neck	Trunk	Arm	Hand	Leg	Foot	Total
Pregnant at surgery	1	5	2	1	13	1	23
Not pregnant at surgery	19	47	28	2	162	8	266

The survey included a postal questionnaire sent to 191 patients, all of whom had undergone removal of a melanoma since 1967 and were known to be alive at the time of the review; 140 (73%) responded. The combination of the replies and up-to-date register entries meant that for 181 of the 290 patients specific information was available about pregnancy subsequent to a melanoma.

Statistical methods employed included the χ^2-test for assessing the difference in the involvement of different sites between those pregnant at the time of surgery and those not. Standard life table and survival analysis techniques (Peto *et al.* 1977) were used to assess differences in prognosis between the different subgroups, resulting in the Mantel–Cox statistic. Programme PIL of BMDP statistical package (Dixon 1983) was employed for these analyses. Prognosis was taken to mean survival to death and also, separately, as 'survival' to recurrence, both timed from the removal of the melanoma. Very occasionally some items of information were missing, e.g. it was known that a patient had died from melanoma but the precise type and date of first recurrence was not recorded. In consequence, in these circumstances, the patient was excluded from the subsequent relevant analysis. This accounts for small differences in numbers in the groups analysed.

Results

Age

There were 23 patients who were pregnant at the time of surgery; their mean age was 28·7 years. A further 23 women became pregnant after the removal of their melanoma; they had an average age of 27·3 years. The average age of the 243 patients who were neither pregnant at the time of surgery or after was 32·3 years.

Site

In 57% of patients pregnant at the time of surgery, the lesions occurred on the leg, whereas in 61% of the non-pregnant group the lesion occurred at this site. The trunk, another site traditionally associated with a poor prognosis, was involved in 18% of the non-pregnant group and 22% of the pregnant group. Acral lesions occurred in 9% of the pregnant group and 4% of the non-pregnant. Analysis showed no difference in the distribution of melanoma sites between the two groups (χ^2=0·44, d.f.=2). The sites are shown in Table 1, but for statistical purposes the upper limb sites were combined, as were the lower limb sites.

Pregnant at time of surgery

Survival. Of the 23 patients included in this analysis, 6 (26%) died from melanoma, on average 53·5 months after surgery (range 10–88 months). Of the 241 non-pregnant women included in this analysis 31 (13%) died of the disease, on average 50·6 months after surgery (range 7–200 months). The estimated survival functions for the two groups are given in Fig. 1. The less favourable survival for the pregnant group is not statistically significant. These figures were then analysed to see if they related to the thickness of the melanoma. Table 2 gives the mean values for the patients pregnant at the time of surgery and those not, each subdivided into those who died and those who survived. Although the mean thickness was less in the pregnant patients the difference was not significant, indicating that the difference in survival is not due to difference in thickness between the groups.

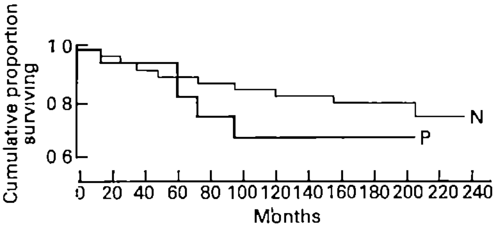

Fig. 1. Survival curve; pregnant at time of surgery (P) against not pregnant (N). Mantel–Cox statistic=1·17, P=0·28.

Table 2. Thickness of melanoma (in mm) in relation to survival and recurrences in pregnant and non-pregnant women

	Survived	Died	Not recurred	Recurred
Not pregnant at surgery	1·72 (1·70) (n=204) t=0·23	3·96 (4·59) (n=30) t=0·64	1·48 (1·33) (n=186) t=0·19	4·15 (4·02) (n=47) t=0·75
Pregnant at surgery	1·62 (1·13) (n=17)	2·62 (2·05) (n=5)	1·54 (1·11) (n=16)	2·78 (2·03) (n=5)
Not pregnant after surgery	1·76 (1·67) (n=104) t=0·07	4·01 (4·67) (n=29) t=0·51	1·59 (1·56) (n=96) t=0·43	3·91 (4·25) (n=35) t=0·91
Pregnant after surgery	1·73 (1·38) (n=20)	2·60 (1·51) (n=3)	1·76 (1·40) (n=18)	2·14 (1·48) (n=5)

Results are mean (SD) values. n shows the number of patients in whom thickness could be assessed.
None of the t values was statistically significant.

Recurrence. Of the 22 patients who were pregnant at the time of surgery, 6 (27%) had recurrences, five within the first year. The average time after surgery was 16·7 months (range 4–65 months). Of the 240 non-pregnant patients included in this analysis, 48 (20%) had a recurrence, 25 in the first year. The average time following surgery was 25·5 months (range 3–184 months). These differences were not statistically significant (Fig. 2). The effect of thickness on recurrences was analysed separately and Table 2 shows the mean thickness according to recurrence in the pregnant and non-pregnant groups. The results again indicate that the differences in survival are not due to differences in thickness.

Pregnant after surgery

Survival. Of the 160 patients included in this analysis 23 became pregnant after surgery, three of them (13%) died of the disease, on average 35·0 months after surgery. Of the 137 women who did not become pregnant after surgery, 29 (21%) died of the disease, on average 51·6 months after surgery (range 7–200 months). The estimated survival curves for these groups are shown in Fig. 3; the differences were not statistically significant. The effect of thickness was also estimated; it was shown to have no effect on survival (Table 2).

Recurrence. Of the 23 patients who became pregnant after removal of a melanoma 5 (22%) subsequently developed a recurrence. The average interval after initial surgery was 25·6 months and all occurred within the first 4 years (range 11–39 months). Of the 136 patients analysed who had not become pregnant, 37 (27%) had a recurrence with an average period following surgery of 27·3 months (range 3–184 months), 31 of them within the first 4 years. The estimated survival curves by recurrence are shown in Fig. 4; there was no statistically significant difference between the groups. Thickness of the melanoma had no significant effect on survival (Table 2).

Discussion

The effects of pregnancy, or hormone adminis-

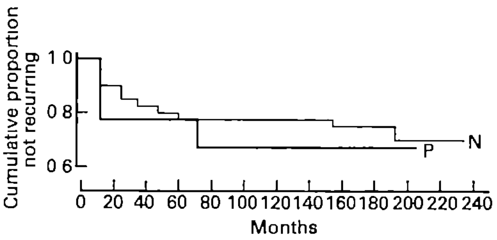

Fig. 2. Survival curve for recurrence; pregnant at time of surgery (P) against not pregnant (N). Mantel–Cox statistic=0·58, P=0·44.

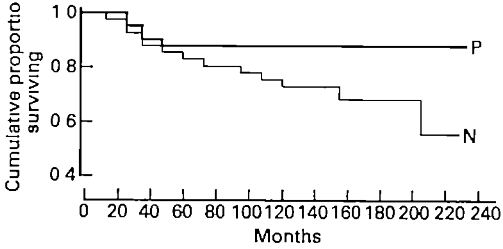

Fig. 3. Survival curve; pregnant after surgery (P) against not pregnant (N). Mantel–Cox statistic=1·57, P=0·21.

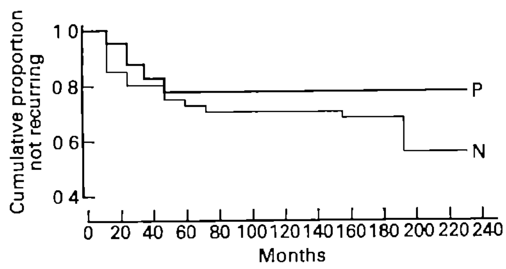

Fig. 4. Survival curve for recurrence; pregnant after surgery (P) against not pregnant (N). Mantel-Cox statistic=0·77, P=0·38.

tration, on the behaviour of melanoma is unclear. Although the tumour occurs equally in men and women, the latter tend to have longer survival rates (Shaw *et al* 1978; Reintgen *et al.* 1983). Large clinical series on the effect of pregnancy on melanoma are conflicting in their conclusions: George *et al.* (1960), Elwood & Coldman (1978) and Houghton *et al.* (1981) have all reported that melanoma in pregnancy behaves the same as in non-pregnant patients, matched for age and site. Others even report regression of melanoma after pregnancy (Sumner 1953; Allen 1955; Lerner *et al.* 1979). On the other hand, some authors strongly advocate termination of pregnancy if concurrent melanoma is diagnosed (Clayton 1946; Pack & Scharnagel 1951; Hadley 1952; Byrd & McGanity 1954; Riberti *et al.* 1981). Shiu *et al.* (1976) found that pregnancy had an adverse effect in stage 2 disease but not in stage 1. Lerner *et al.* (1979) reported the adverse effect on melanoma of hormone administration, as did Ellerbrook (1968). Shaw *et al.* (1978) found no statistical difference of puberty, menopause or oestrogen administration on 5-year survival rates.

Increased pigmentation occurs in pregnancy and existing benign naevi become larger and darker as a result of the increased levels of oestrogen, progesterone and melanin-stimulating hormone (Winton & Lewis 1982), although no true oestrogen receptors have been consistently shown in human melanoma (McCarty *et al.* 1980).

Pre-menopausal women have better survival rates than the post menopausal (Shaw *et al.* 1978), as do parous patients, compared with nulliparous (Hersey *et al.* 1977; Shaw *et al.* 1978). Hersey *et al.* (1977) suggested the known presence of fetal antigens on melanoma cells and the pregnant woman's subsequent immunization to these fetal antigens during pregnancy as an explanation for the better survival rates in parous patients. This may also explain why, following the diagnosis of melanoma, women with subsequent pregnancies have the same prognosis as non-pregnant patients (Sutherland *et al.* 1983; Reintgen *et al.* 1985).

Our series did not show any significant effects of pregnancy on melanoma either concurrent with, or subsequent to, the diagnosis of the tumour.

After treatment of melanoma in this Unit it is known that over 60% recur within 2 years of initial diagnosis, and 87% within 5 years (Griffiths & Briggs 1984). In the present series most recurrences occurred within 3 years of primary treatment, with an average time between surgery and pregnancy of 40 months in those women who had no further problems. We therefore suggest that women who develop a melanoma should not become pregnant within 3 years of treatment. Termination of pregnancy is not indicated and the chance of transplacental spread to the fetus is so rare (Moss & Briggs 1986) as to be safely disregarded.

Acknowledgment

We thank the consultant reconstructive plastic surgeons at Frenchay Hospital for permission to review patients under their care.

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2308 second trimester terminations using extra-amniotic or intra-amniotic prostaglandin E_2: an analysis of efficacy and complications

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Summary. A total of 2308 mid-trimester terminations using PGE_2 extra-amniotically (1608) or intra-amniotically (700) has been analysed for efficacy and immediate and early morbidity. The mean induction-to-abortion intervals were similar for the two routes. Overall, 67% of the patients were in hospital for 1 night. Morbidity rates were similar for the two administration routes and were no higher than those reported for second trimester terminations using dilatation and evacuation. Minor side-effects of vomiting occurred in 1006 (44%) and diarrhoea in 320 (14%). Forty (1·7%) lost more than 500 ml of blood during termination and 13 (0·6%) were transfused. Major complications were extremely rare and genital tract trauma only occurred in 4 (0·17%) and proven pelvic infection in 2 (0·08%) patients. Thirty-three (1·4%) were re-admitted and required a surgical evacuation of the uterus. Since long-term complications have been assessed for this method of termination and found to be infrequent, we see no reason to consider a change in methods for second trimester terminations.

Since the introduction of the Abortion Act 1967 in England and Wales, the number of terminations during the second trimester has declined from 22% in 1968 (OPCS 1970) to 19% in 1977 (OPCS 1979); during the subsequent years, the proportion has remained relatively unchanged (OPCS 1987). Figures from a survey by the Royal College of Obstetricians and Gynaecologists in 1982 (Stanwell-Smith 1984) indicated that the methods of termination used include 27% performed by the minor surgical methods and 68% using prostaglandins, most of them involving intrauterine instillation techniques.

Virtually all reports have indicated that terminations in the second trimester results in greater morbidity than occurs with first trimester termination, and reports from the USA suggest that late termination using prostaglandin results in more complications than occur with cervical dilatation and surgical evacuation (Grimes *et al.* 1980). We have analysed the results of 2308 consecutive mid-trimester abortions induced using intrauterine prostaglandin E_2 (PGE_2) conducted over a 12-year period in our unit.

Subjects and methods

Between January 1976 and December 1987, 2308 patients admitted for pregnancy termination in the second trimester under grounds 2 and/or 3 of the Abortion Act 1967 were managed

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Table 1. Characteristics of 2308 patients undergoing mid-trimester prostaglandin termination of pregnancy

Characteristic	Intra-amniotic (n = 700) n (%)	Extra-amniotic (n = 1608) n (%)	Total (n = 2308) n (%)
Age group (years)			
<16	33 (5)	109 (7)	142 (6)
16–20	332 (46)	708 (44)	1040 (45)
21–25	174 (25)	340 (21)	514 (22)
26–30	66 (10)	200 (12)	266 (11)
31–35	49 (7)	127 (8)	176 (8)
35–40	34 (5)	80 (5)	114 (5)
>40	12 (2)	44 (3)	56 (3)
Mean age (SD)	22·3 (6·6)	22·7 (7·1)	
Parity			
0	480 (69)	1028 (64)	1508 (65)
1–3	201 (29)	530 (33)	731 (32)
4+	50 (3)	19 (2)	69 (3)
Mean parity (SD)	0·6 (1·1)	0·8 (1·2)	
Previous termination	80 (11)	170 (11)	250 (11)
Marital status			
Single	508 (73)	1062 (66)	1570 (68)
Married	125 (18)	386 (24)	511 (22)
Previous marriage	67 (9)	160 (10)	227 (10)
Gestation (weeks)			
12–13	12 (2)	180 (11)	192 (8)
14–15	129 (18)	681 (42)	810 (35)
16–17	230 (33)	590 (37)	820 (36)
18–19	260 (37)	139 (9)	399 (17)
≥20	69 (10)	18 (1)	87 (4)
Mean gestation (SD)	17·1 (1·8)*	15·3 (1·6)*	

*Significantly different between the two groups $P \leq 0{\cdot}001$.

using either extra-amniotic or intra-amniotic injections of PGE$_2$. Most of the patients were treated extra-amniotically, but the route of administration was generally selected according to the gestation and surgeon's preference, with other individual patient factors taken into consideration. The intra-amniotic route was generally preferred at later gestations because the procedure is technically difficult before 14 weeks. Data on patient characteristics, gestation and abortion method (Table 1) were recorded on purpose-designed record sheets. The same forms were used for recording outcome and complications.

All patients were treated with PGE$_2$ on the day of admission. Extra-amniotic PGE$_2$ was administered by giving 1·5 mg or 2·5 mg of PGE$_2$ dissolved in 10 ml of 6% viscous methyl hydroxyethyl cellulose as a single injection via a 14 French gauge Nelation catheter passed through the cervix and immediately withdrawn after the injection (MacKenzie & Embrey 1976). Intra-amniotic administration involved the technique described by MacKenzie *et al.* (1974*a*); 5 mg or 10 mg PGE$_2$ were injected as a single dose after which the needle was withdrawn. All the patients received an intravenous infusion of oxytocin (100 m-units/min) beginning 6 h after PGE$_2$ administration and this was maintained until abortion. The next morning, if abortion had not occurred or was not imminent, contractions were augmented with more PGE$_2$ or by increasing the oxytocin infusion rate. Premedication was not given to patients treated extra-amniotically, but some treated intra-amniotically received diazepam, 5–10 mg intravenously, shortly before the injection. Papaveretum, 20 mg, and chlorpromazine, 25 mg, were given intramuscularly for analgesia when required.

Following expulsion of the fetus, ergometrine, 500 µg, or oxytocin, 5 units, were given intramuscularly. Surgical uterine evacuation was

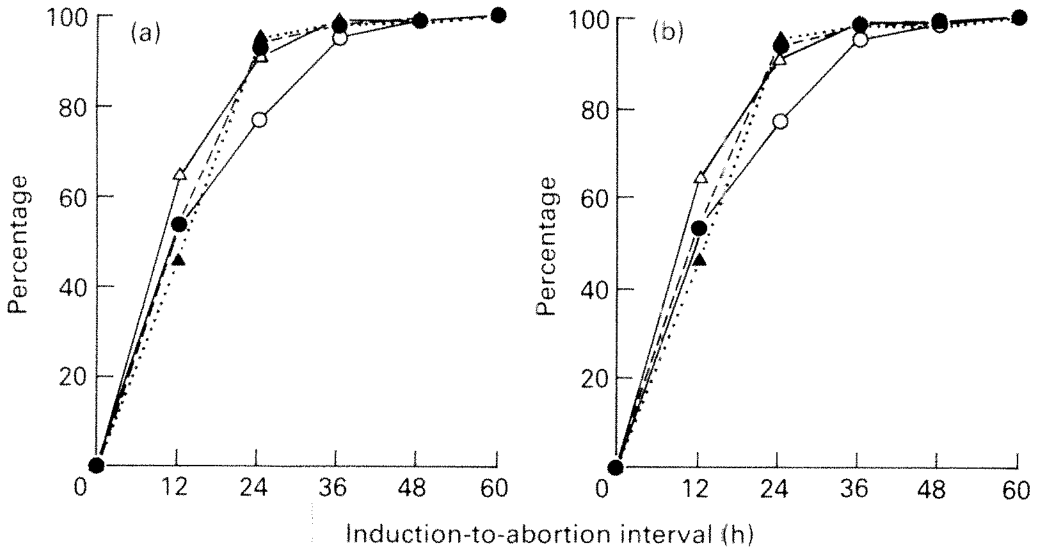

Fig. 1. Cumulative induction-to-abortion intervals for extra-amniotic PGE$_2$ 2·5 mg (△) [*n* = 1290], 1·5 mg (○) [*n* = 318], and intra-amniotic PGE$_2$ 10 mg (●) [*n* = 200], and 5-mg (▲) [*n* = 500] in (a) nulliparae and (b) multiparae.

only performed if the placenta was retained or seemed incomplete, or if placental tissue was palpated through the cervix at routine post-abortion vaginal examination. Blood loss at abortion was estimated to the nearest 100 ml, and transfusions were only given when clinically indicated. Antibiotics were administered if infection was clinically suspected after the appropriate bacteriological specimens had been collected, or if the induction to abortion interval was unduly prolonged, or if indicated for some pre-existing condition. Non-sensitized Rhesus-negative patients routinely received anti-D immunoglobulin during the first 24 h following abortion. Patients were not followed up routinely but all readmissions were directed to our unit, the gynaecological unit serving more than 95% of the local population.

Results

There were no statistically significant differences between the two treatment groups with regard to age, marital status, parity or previous termination (Table 1). The gestational age in the intra-amniotic group (mean 17·1, SD 1·8 weeks) was greater than in the extra-amniotic group (mean 15·3, SD 1·6 weeks); 12 terminations were performed at 21 weeks gestation and one at 22 weeks gestation.

In no patient was the prostaglandin technique unsuccessful in provoking abortion, and resort to another termination method was never required.

Efficacy

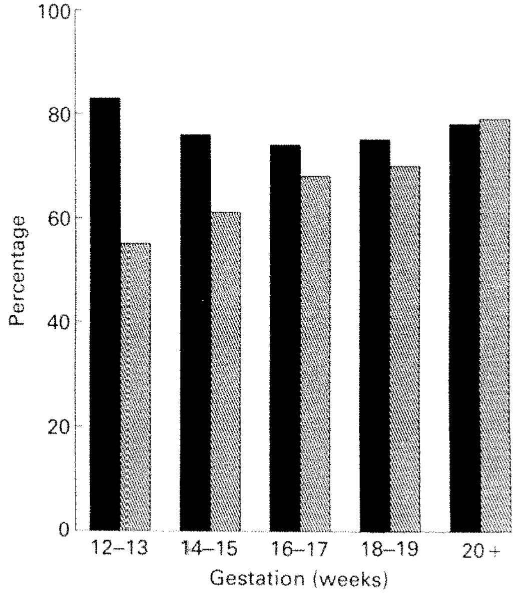

Fig. 2. Frequency of immediate complete abortion by gestation in extra-amniotic (▨) [*n* = 1608], and intra-amniotic (■) [*n* = 700] terminations.

Cumulative abortion rates for the two adminis-

Table 2. Frequency of side-effects and complications after mid-trimester termination of pregnancy

	Intra-amniotic (n = 700) n (%)	Extra-amniotic (n = 1608) n (%)	Total (n = 2308) n (%)
Vomiting	274 (39)	732 (45)	1006 (44)
Diarrhoea	36 (5)	284 (17)	320 (14)
Blood loss $amn500 ml	11 (1·5)	29 (1·8)	40 (1·7)
Transfusion	5 (0·7)	8 (0·5)	13 (0·6)
Genital trauma	2 (0·3)	2 (0·1)	4 (0·17)
Pelvic infection	3 (0·4)	5 (0·2)	8 (0·4)
Readmission for surgical evacuation	8 (1·1)	25 (1·1)	33 (1·4)

tration routes and different PGE_2 doses are illustrated in Fig. 1. The longest induction-to-abortion interval was 60 h. The mean interval for the extra-amniotic group was 14·8 h (SD 9·2) and for the intra-amniotic group 14·8 h (SD 7·2).

The length of gestation did not influence the mean induction-to-abortion interval, but the interval was significantly longer in nulliparae at 15·7 h (SD 8·3) than in multiparae at 13·1 h (SD 7·3) ($P \leq 0{\cdot}01$). Oxytocin augmentation was given to 92·5% of the intra-amniotic group compared with 88·5% of the extra-amniotic group. In the extra-amniotic group, treatment with 2·5 mg of PGE_2 resulted in a significantly shorter mean induction-to-abortion interval at 14·0 h (SD 8·6) than with 1·5 mg of PGE_2 at 15·7 h (SD 10·9) ($P \leq 0{\cdot}001$). Similarly 10 mg of PGE_2 intra-amniotically resulted in a mean interval of 14·5 h (SD 6·9) compared with a mean interval of 15·5 h (SD 8·5) associated with 5 mg of PGE_2 ($P \leq 0{\cdot}001$).

Abortion within 24 h occurred in 89·4% of the intra-amniotic group compared with 83·2% of the extra-amniotic group. In all, only 2% of the intra-amniotic group and 3·1% of the extra-amniotic group took longer than 36 h to abort; 10% of each group required additional oxytocic augmentation to achieve abortion.

Incomplete abortion

Figure 2 illustrates the frequency of complete abortion according to gestation and route of PGE_2 administration. Doses of PGE_2 used, patients' age and parity did not influence the results. There was an association between route of PGE_2 administration and the frequency of incomplete abortion, with 35% of the extra-amniotic group needing a surgical evacuation of the uterus compared with 25% of the intra-amniotic group.

Side-effects

Vomiting was the most common side-effect. 732 women (45·5%) in the extra-amniotic group had at least one episode of vomiting compared with 274 (39·0%) in the intra-amniotic group (Table 2); the corresponding numbers for diarrhoea were 284 (17·6%) and 36 (5·1%). These side-effects were not related to gestational age, parity, induction-to-abortion interval, or dose of PGE_2 given. There was, however, a direct association with need for analgesia.

A pyrexia of 37·5°C on at least one occasion during the abortion process was recorded in 15% of the total sample studied, only 2% of whom developed a higher temperature. Four patients experienced a severe 'prostaglandin reaction' which responded to supportive treatment alone, and abortion was induced in the usual way. Analgesia was given to 2030 (88%) patients during the contractile phase. The need for analgesia was not influenced by length of gestation, age, PGE_2 dose or route of administration; more nulliparae (92·2%) required analgesia than multiparae (80·0%) ($P \leq 0{\cdot}001$).

Table 3. Length of stay in hospital in 2308 patients undergoing termination according to route

Length of stay (Days)	Intra-amniotic (n = 700) n (%)	Extra-amniotic (n = 1608) n (%)
1	453 (65·2)	1075 (67·0)
2	223 (32·1)	473 (29·5)
3	19 (2·7)	56 (3·5)
Tubal ligation	5	4

Morbidity

Blood loss. Overall, 40 (1·7%) patients lost more than 500 ml and 13 (0·6%) required a transfusion (Table 2). These cases were evenly distributed between the extra- and intra-amniotic groups. The number of patients losing more than 500 ml at termination was not significantly affected by gestation, parity, or induction-to-abortion interval. Of those who had an incomplete abortion 5% lost >500 ml of blood.

Infection. Overall, 45 (1·9%) patients received antibiotics whilst in hospital, but only two (0·08%) had proven sepsis. This was due to a β-haemolytic streptococcal infection in one and a *Clostridium welchii* infection in the other. Both patients recovered uneventfully after antibiotic treatment. In six (0·3%) patients, pelvic infection was later suspected.

Genital tract trauma. Four (0·17%) patients sustained some damage to the genital tract. The first was a 25-year-old nullipara at 24 weeks gestation treated with 2·5 mg extra-amniotic PGE$_2$; she aborted uneventfully after 10 h. At surgical evacuation a broad ligament haematoma was suspected which was managed conservatively without complication. Second was a 17-year-old nullipara at 15 weeks gestation treated with 2·5 mg extra-amniotic PGE$_2$ who required additional augmentation with intramuscular 15-methyl PGF$_{2\alpha}$ after 24 h. She aborted after 55 h and at evacuation was found to have a broad ligament haematoma which was managed conservatively without complication. The third patient was a 24-year-old nullipara at 17 weeks gestation treated with 5 mg intra-amniotic PGE$_2$, she was given additional PGE$_2$ extra-amniotically after 24 h and aborted after 60 h. At evacuation a posterior cervical tear was confirmed which was surgically repaired. The fourth patient was a 25-year-old multipara at 18 weeks gestation treated with 10 mg intra-amniotic PGE$_2$ who aborted after 36 h having been augmented with extra-amniotic PGE$_2$. She developed lower abdominal pain after abortion and a diagnosis of broad ligament haematoma was made. She improved with conservative treatment but developed a deep vein thrombosis and was hospitalized for a further 10 days on anti-coagulation therapy: a complete recovery was made.

Duration of hospital admission

Table 3 shows the number of nights spent in hospital during the abortion treatment. The mean number of nights in hospital for the extra-amniotic group was 1·38 days (SD 0·72), compared with 1·43 days (SD 0·83) for the intra-amniotic group; 67% of the patients were in hospital for only 1 night. Fourteen patients had prolonged stays in hospital because they were sterilized by tubal ligation immediately after the abortion.

Readmission

Overall, 41 (1·8%) patients were readmitted to hospital after the termination (Table 2). Thirty-three (1·4%) had excessive bleeding managed by uterine curettage, and eight (0·4%) with suspected, but unproven, pelvic infection. Patients were equally distributed between the two administration groups. Half the re-admissions occurred within 7 days of termination, and the remainder over the next 5 weeks.

Discussion

The results represent a marked improvement on those we reported previously (MacKenzie *et al.* 1974*b*) of 626 consecutive mid-trimester abortions induced with intrauterine PGE$_2$ and PGF$_{2\alpha}$ using a variety of dosage protocols. The mean induction-to-abortion interval of 14·8 h for both routes of PGE$_2$ administration is markedly less than the 16·7 and 17·2 h we reported in 1974 for the two routes. Morbidity rates have similarly improved with a reduction in excessive haemorrhage from 6·1% to 1·9%, transfusion requirement from 1·3% to 0·6%, genital tract trauma from 0·5% to 0·2%, and proven clinical sepsis from 0·3% to 0·08%. Our very low rate of confirmed pelvic sepsis (0·08%) and the overall use of antibiotics (1·9%) for prophylaxis required in patients with pyrexia is testament to our approach not to give antibiotic as a routine (MacKenzie & Fry 1981*a*).

There is a lack of similar large series of mid-trimester terminations using intrauterine prostaglandins with which to compare our results. The report by the RCOG (Stanwell-Smith 1984) on 2766 second trimester abortions, which included intra-amniotic and extra-amniotic prostaglandin instillation methods, does not provide data which allow adequate analysis by termination method. It was, however, concluded that the need for readmission and re-evacuation of the uterus was more common after extra-amniotic prostaglandin administration compared with other methods; our values of 1·2% for the extra-amniotic group and 2·0% for the intra-amniotic group, resulting from a policy of selective curettage immediately after expulsion of the conceptus rather than routine curettage, are much lower than those reported for the total group in the RCOG study of 1·4–5·8% (Stanwell-Smith 1984). Indeed, we reported a readmission rate for re-evacuation of 2·7% after 670 first trimester aspiration termination under general anaesthesia (MacKenzie & Fry 1981*b*). We thus challenge the recommendation of that report for routine post-abortal curettage following prostaglandin terminations.

Overall, there were few differences in induction-to-abortion interval and morbidity rates between the two routes of administration using the different dosage regimens; as expected, however, patients treated with the larger doses of PGE_2 with both routes had shorter induction-to-abortion intervals. The intra-amniotic technique resulted in a greater proportion of abortions within 24 h, with a lower frequency of gastrointestinal side-effects, which represents genuine advantages. For technical reasons, the intra-amniotic route was used infrequently before 15 weeks gestation: but with the introduction of small mobile real-time sonar scanning machines, this route is more readily employed at the beginning of the second trimester. Furthermore, with continuous vision it is possible to avoid the 'prostaglandin reaction' that occasionally occurs immediately after the prostaglandin injection due to inadvertent instillation into decidual blood vessels leading to a large dose of prostaglandins reaching the systemic circulation causing acute circulatory collapse.

There have been a number of claims, frequently from the USA, that termination in the second trimester by dilatation and evacuation is safer than intrauterine prostaglandin methods (Grimes *et al.* 1980: Cadesky *et al.* 1981: Cates *et al.* 1982: Peterson *et al.* 1983). Often these claims have been made using analyses of pooled data from a number of institutions using intra-amniotic $PGF_{2\alpha}$ for comparison (Grimes & Cates 1982). Our results from a single centre with much experience in both intra-amniotic and extra-amniotic PGF_2 compare very favourably with those reported for dilatation and evacuation. Our overall transfusion rate at 0·6% is high but has declined in recent years and compares with 0·2% (Grimes & Cates 1979; Peterson *et al.* 1983) and 1·3% (Hodari *et al.* 1977) for dilatation and evacuation. But suspected intra-uterine sepsis after dilatation and evacuation appears to be higher at 1·04% (Cates *et al.* 1982) and the need for readmission for re-evacuation higher at 3·0% (Edelman *et al.* 1974). The frequency of genital tract trauma in our study was 0·17%. This is much lower than rates of 0·3–1·0% for cervical laceration and up to 0·4% for uterine perforation that have been quoted for dilatation and evacuation (Hodari *et al.* 1977; Berger & Keith 1982; Peterson *et al.* 1983). Overall, the major complication rate in our series was 0·25% (genital tract trauma in four and confirmed pelvic sepsis in two) which is similar to that reported by Cates *et al.* (1982) in 2204 dilatation and evacuation procedures and less than the 0·44% reported by Barr (1978) in 900 procedures, by Peterson *et al.* (1983) of 0·6% in 11 747 procedures, and Hodari *et al.* (1977) of 1·65% in 2 490 procedures. We acknowledge, however, that different definitions of 'major complication' have probably been used in each of the studies cited. Nevertheless, none of our patients required a hysterectomy or laparotomy which occurred in both the large single-centre series reported by Peterson *et al.* (1983) and Hodari *et al.* (1977). Unfortunately there have been no worthwhile prospective randomized trials to compare the two different treatments; comparative observational data must therefore be viewed with reservation.

Delayed morbidity after pregnancy termination represents an important aspect of any termination procedure. A number of prospective long-term studies have been reported after a mid-trimester termination using prostaglandins which have failed to show any significant adverse effect on subsequent menstrual function (MacKenzie & Hillier 1975), fertility (MacKenzie & Fry 1988), and pregnancy outcome (MacKenzie & Hillier 1977). There is a dearth of similar information after dilatation and evacuation in the second trimester. It has been suggested that surgical dilatation of the cervix beyond 10 mm might compromise subsequent cervical competence, but apart from the series reported by Beckhuizen *et al.* (1982) of second trimester aspirotomy requiring 10 mm cervical dilatation only, in most reported series of dilatation and evacuation a much greater surgical dilatation is used (Hodari *et al.* 1977; Peterson *et al.* 1983; Stanwell-Smith 1984). There must remain some anxiety about possible loss of cervical integrity and subsequent pregnancy outcome compromise following this procedure.

In recent years, vaginal administration of prostaglandin analogues for second trimester abortion has been reported (Mandelin & Kajanoja 1978; Embrey 1982; Cameron & Baird 1984). To date there do not appear to be any definite advantages over the techniques described in this paper. By avoiding intrauterine injections of prostaglandins, post-abortal sepsis might be reduced and inadvertent systemic injection will be circumvented. A more exciting new approach recently reported combines the use of an anti-progestational agent given before a lower dose of prostaglandins: this results in fewer side-effects and shorter induction-to-abortion intervals (Selinger *et al.* 1987). Further work using this concept is needed. Although our results for hospital stay are better than those reported by the RCOG (Stanwell-Smith 1984), this new regimen could lead to a 'day-care' method for second trimester prostaglandin induction of abortion.

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Comparison of the Foley catheter and dinoprostone pessary for cervical preparation before second trimester abortion

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Summary. The Foley catheter and a 3 mg dinoprostone pessary (Prostin E_2) were compared as methods for cervical preparation before second trimester dilatation and evacuation. The catheter was well tolerated and provided significantly greater change in cervical dilatation and improved cervical compliance. The Foley catheter would seem to provide a readily available and efficacious means of cervical preparation.

Dilatation and evacuation is gaining increasing acceptance as the technique of choice for termination of pregnancy in the second trimester (Grimes & Schulz 1985). Although there is a dearth of good studies examining the long-term sequelae of this procedure, there is considerable concern about the effects of acute mechanical dilatation of the cervix, and new techniques for cervical preparation are continuing to be assessed. The use of prostaglandins and their analogues, laminaria tents, balloon catheters, and Lamicel have all been investigated. In this unit both the Foley catheter and dinoprostone (Prostin E_2, Upjohn) pessaries have been utilized. We have studied the relative efficacy of these two methods in priming the cervix before second trimester pregnancy termination.

Subjects and methods

The women entered into the study were consecutive referrals from the District Pregnancy Advisory Service. All were at between 12 and 16 weeks gestation as determined by both a reliable menstrual history and pelvic examination. Any discrepancy between these was resolved by ultrasound examination.

Ethics committee approval was obtained and each woman gave fully informed verbal consent. No exclusions were made and no refusals were encountered. Details of age, race, medical, obstetric and gynaecological history were recorded and the women were assigned to treatment with either a Foley catheter or dinoprostone pessaries on the basis of an odd or even terminal digit of their hospital number. The two treatment groups thus formed were the catheter group comprising 21 women and the pessary group comprising 23 women. The women were seen at admission, 24 h before operation. On pelvic examination a Cuscoe's speculum was introduced and the cervix swabbed with Savlodil solution (chlorhexidine 0·015%/cetrimide 0·15%). With the aid of a tenaculum on the anterior lip of the cervix the dilatation of the internal os was assessed with a Hegar dilator. In this study, introduction of the largest dilator was attempted first. The diameter of the dilator was then reduced in 0·5-mm steps until a dilator could be introduced without force. This method excluded any involuntary dilatation.

In the women assigned to the catheter group, a size-14 Foley catheter was inserted into the cervical canal to a depth of 3 to 4 cm. The balloon, which was thus placed beyond the internal os, was then inflated with 25 ml of water. The women in the pessary group had a 3-mg dino-

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Table 1. Characteristics of the women in the study

	Catheter group ($n = 21$)	Pessary group ($n = 23$)
Age (years)	25·1 (4·9)	22·5 (6·1)
Gestational age (weeks)	13·8 (1·2)	13·5 (1·2)
Nulliparae	9	12
Multiparae	12	11

Results are mean (SD) values.

prostone pessary placed in the posterior fornix, and were asked to remain supine for a short period afterwards. In both groups the women were allowed to move freely in the ward before operation. Immediately before premedication the Foley catheter stems were cut so deflating the balloon and allowing removal of the catheter without further vaginal examination.

In theatre, the operators (D.B.P. and P.W.R.) were thus blinded to the method of cervical preparation. After routine induction of general anaesthesia, and before the procedure, the cervical dilatation was assessed again as described above. The operator then noted the ease with which he obtained the further dilatation necessary to accomplish the evacuation. This assessment of cervical 'compliance' was described on a scale of 1 to 5 where 1 represented 'very easy' and 5 'very difficult'. Routine dilatation and evacuation was performed and complications or special features of the procedure were noted.

The large range in amniotic fluid volume between 12 and 16 weeks gestation precludes accurate estimation of the blood loss. However, any undue haemorrhage was noted by the surgeons, both of whom had considerable experience with the technique. The cervix was carefully inspected at the end of the procedure. On the next day the women were interviewed and questioned directly about any symptoms experienced before or after the procedure.

Comparison of the data used Student's t-test and χ^2-test where appropriate.

Results

The catheter group included 21 women, and the pessary group included 23 women. The gestational ages, and the ages of the women were similar in the two groups ($t = -1{\cdot}56$, $P = 0{\cdot}13$) (Table 1). There was no significant difference in parity between the two groups ($\chi^2 = 0{\cdot}10$).

Although the cervical dilatation before preparation was similar in the two groups (Table 2), at the start of the operation the increase in dilatation was significantly greater in the catheter than in the pessary group ($t = -3{\cdot}2$; $P = 0{\cdot}003$). Furthermore the ease with which further dilatation was accomplished, the cervical compliance, was significantly improved in the catheter compared with the pessary group ($t = -5{\cdot}02$; $P = 0{\cdot}001$).

Five women complained of low abdominal cramps before surgery (four in the catheter and one in the pessary group). Only one woman requested analgesia pre-operatively. She had a catheter and this was removed some hours before operation but apparently without loss of efficacy. Pyrexia occurred in one woman postoperatively where a catheter had been used but the pyrexia had been present on admission and was thought to represent an intercurrent viral illness. Postoperative recovery was otherwise uneventful in this patient and no pathogens were cultured from genital tract swabs. Tenaculum tears occurred in two women, one in each group. A bucket-handle tear occurred in one woman in the pessary group. She had had two caesarean sections for failure to progress in labour. As it proved so difficult to dilate the cervix a hysterotomy was performed.

Interviews conducted after the operation did not reveal any further complaints associated with either procedure. In particular the women in the catheter group did not consider the method unduly intrusive.

Conclusions

That the cervix is an obstacle to the emptying of the uterus is evidenced by the many methods advocated to overcome its resistance. The fre-

Table 2. Cervical characteristics before and after priming with the Foley catheter or a dinoprostone pessary

	Catheter group ($n = 21$)	Pessary group ($n = 23$)
Dilatation at admission (mm)	3·2 (1·2)	3·7 (1·9)
Dilatation in theatre (mm)	10·4 (2·1)	8·7 (2·1)
Change in dilatation (mm)	7·2 (1·9)	5·0 (2·3)*
Compliance score	4·4 (0·9)	2·8 (1·1)

Results are mean (SD) values.
* $t = -3{\cdot}2$ (42 d.f.) $P = 0{\cdot}003$.
** $t = -5{\cdot}02$ (42 d.f.) $P = 0{\cdot}001$.

quency of cervical injury after induced abortion is difficult to ascertain depending as it does on definition, time of assessment of the cervix in relation to the procedure, and difficulties in detecting tissue damage. Edstrom (1975) reported rates ranging from 0·3 to 4·9% and, more recently Heisterberg & Kringelbach (1987) found that 0·1% of 5851 women had sustained cervical injury during suction termination. Although there is no consensus view concerning the long-term sequelae of dilatation and evacuation (Savage 1982) there has been concern about consequent cervical incompetence and preterm delivery. Hulka *et al.* (1974) reported that dilatation of the cervix beyond 9 mm represented 'tearing of the internal os rather than true dilatation' and Johnstone *et al.* (1976) tentatively concluded from their retrospective study that cervices dilated beyond 12 mm did not show the return to normal patency 6 weeks after operation seen in cervices dilated to <10 mm. These findings are of special note because many of these women are at the beginning of their reproductive lives.

Our results show that better cervical preparation is achieved with the Foley catheter than with a 3 mg dinoprostone pessary. We must, however, be reserved in our conclusions, for ideally the pessary should be inserted some 6 to 8 h before the procedure. Clearly then there is a possibility that the cervix may have 'reconstituted' itself to some degree before operation.

In this small sample there did not appear to be any adverse reaction to the use of the catheter—a finding borne out by our continuing experience with this method. Its mode of action has been postulated to be by a direct mechanical effect or by release of prostaglandins secondary to separation of the fetal membranes (Ezimokhai & Nwabineli 1980).

The readily available and inexpensive Foley catheter may thus offer some advantage over the prostaglandins and their analogues and Lamicel which was found to cause the greatest rate of dilatation within the first 2 h (Nicolaides *et al.* 1983). As the mode of action of the Foley catheter may be similar to that of Lamicel; it should therefore be assessed over a shorter time period than that used in the present study. There are thus possibilities for using this method as part of a daycare procedure.

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Progestogen-induced regression in low-grade endometrial stromal sarcoma. Case report and literature review

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Case report

A 42-year-old nulliparous woman presented with a large pelvic mass. Laparotomy showed a 20-cm partially cystic lesion suspended in the omentum, as well as a smaller solid mass in the rectovaginal space with a protrusion into the pouch of Douglas. The cystic lesion was excised. The ovaries appeared normal and were conserved. Removal of the lesion in the rectovaginal space was delayed until six weeks later, after the histology had been reviewed. This mass was shelled out easily and the capsule left intact.

The past history was significant; ten years previously she had been treated at another hospital for menorrhagia and dysuria of eight months duration. Examination had shown an irregularly shaped uterus, enlarged to the size of a 16-week pregnancy, and a total hysterectomy was performed for presumed fibroids. Histology showed 'stromal endometriosis'.

A year after removal of the pelvic recurrence a chest X-ray showed a new opacity in the left upper lung field. At thoracotomy a 1·5 cm pinkish brown, partly haemorrhagic, well-circumscribed subpleural lesion was removed with a margin of normal lung. Two months later at another abdominal operation a 2·5 cm recurrence was removed from just to the left of the rectum below the pelvic peritoneum. Four months later a computed tomography scan of the pelvis showed recurrent tumour lying behind the bladder and extending out of the pelvis on the left in relation to the psoas muscle.

At this stage the patient had undergone a total of four operations for recurrent or metastatic tumour, and there was evidence of further local recurrence. Treatment was commenced with medroxyprogesterone, 200 mg twice daily by mouth, together with tamoxifen, 10 mg twice daily. Follow-up was aided by serial abdomino-pelvic ultrasound examination at 6-monthly intervals and these showed a slow, somewhat fluctuating decrease in the size of the pelvic mass. No further recurrence or metastasis was evident. The initial scans had shown the mass to measure 7 cm×7 cm×3·5 cm, and after seven years of progestogen treatment the mass was 2·3 cm in maximum dimension. There was a suggestion of cystic change in part of the mass but this could not be distinguished with certainty from adherent bowel. During this period the dose of medroxyprogesterone actually taken by the patient varied according to perceived side-effects of headache and a feeling of 'bloatedness'. It is of interest that after a period of six months during which she took little or no medroxyprogesterone the scan showed a temporary slight increase in the size of the residual mass. Thereafter she took up to twice the recommended dose and this was followed by a further regression. The dose of tamoxifen taken also varied and this was eventually stopped after five years of treatment. There was no obvious relation between the dose of tamoxifen and the rate or maintenance of regression.

Pathological review

Sections from the hysterectomy specimen from 1969 were available for review. The myometrium was extensively infiltrated by a neoplasm composed of small oval to spindle-shaped cells with scanty cytoplasm (Fig. 1). Mitoses were less than one per ten high-power fields. There was a rich network of small vessels within the tumour, imparting a pericytomatous pattern in places. Extensive permeation of thin-walled myome-

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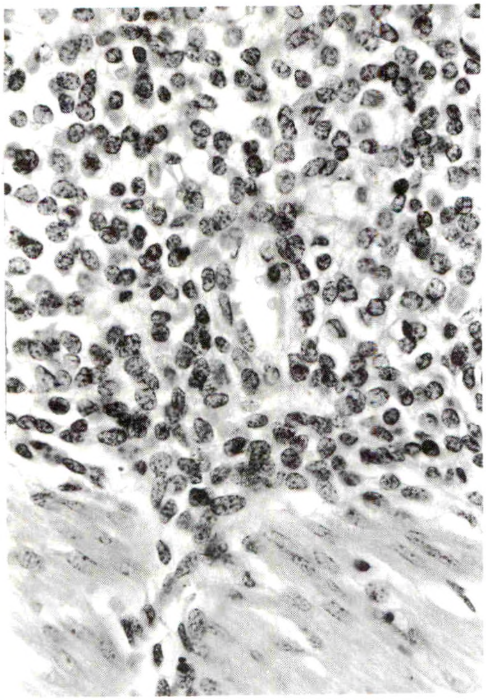

Fig. 1. Endometrial stromal sarcoma infiltrating myometrium. Haematoxylin and eosin ×210.

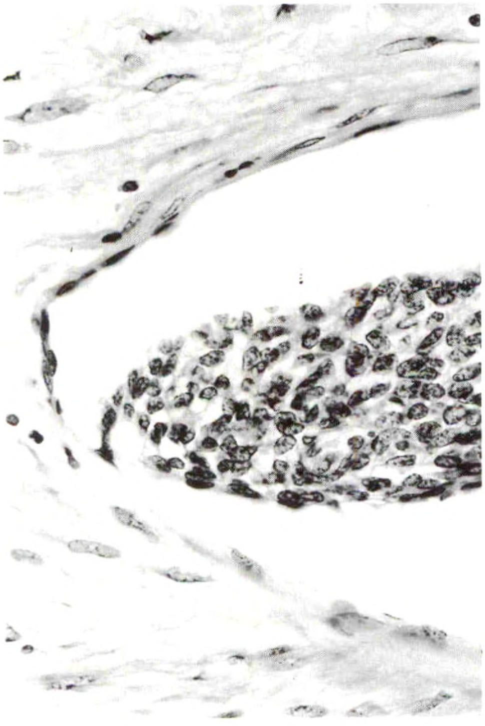

Fig. 2. Permeation of a thin-walled myometrial vessel by sarcoma. Haematoxylin and eosin ×220.

trial vessels was noted (Fig. 2). Although the term 'stromal endometriosis' had been applied, it was clear that the reporting pathologist considered the process to be a neoplasm of low malignant potential.

Sections from the three abdominal and pelvic recurrences as well as from the segmental lung resection (Fig. 3) were similar, with the added features of widespread necrosis and cystic degeneration in the pelvic recurrences, and areas of trabecular epithelioid differentiation in the more fibrotic portions of the pulmonary metastasis. None of the material examined contained well-formed glands. The histological appearances were those of low-grade endometrial stromal sarcoma.

Discussion

Endometrial stromal malignancies are rare sarcomas which may be divided into two groups, low and high grade. The low-grade tumours usually occur in women under 50 years of age and are well differentiated with cells and vasculature resembling the stroma of proliferative endometrium. There have been a few reports of the sustained response of recurrent or metastatic low-grade endometrial stromal sarcoma to high-dose progestogen therapy and we describe a

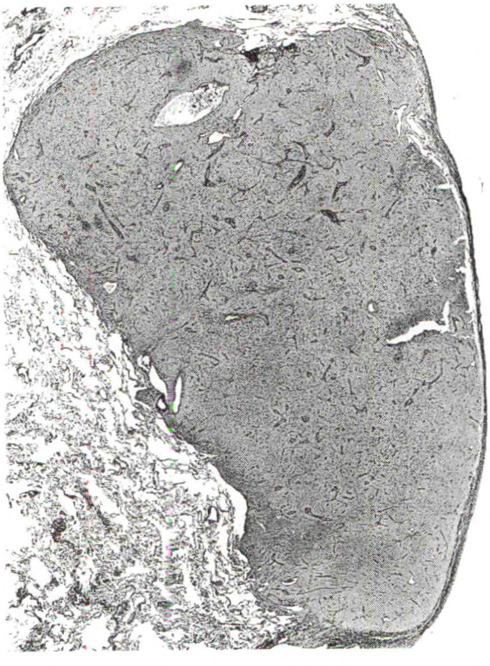

Fig. 3. Subpleural metastasis. Reticulin preparation. ×8.

Table 1. Reported cases of response of low-grade endometrial stromal sarcoma to progestogen therapy

Reference	Age at presentation (years)	Surgery	Interval to first recurrence (years)	Site of recurrence	Agent	Duration (years) and quality of response at the time of reporting	
Pellillo (1968)	22	TAH,USO	0·9	P,L	MPA	2	Complete
Baggish & Woodruff (1972)	42	TAH	2	L	MPA	2·5	Complete
Krumholz *et al.* (1973)	38	TAH	0·75	L	17αHPC,MPA	2·5	Complete
Schmid (1974)	51	TAH,BSO	9	B	17αHPC	1	Complete
Jacobsen & Haram (1975)	35	STH,USO	1	P,V	MPA	3	Complete
Hart & Yoonessi	43	STH,BSO	0·5	P	MPA	1	Complete
Lehrner *et al.* (1979)	21	TAH,BSO	2	SE,L	Meg.A (+cytotoxics)	1	Complete
Brons *et al.* (1980)	27	TAH	11	P	MPA	0·75	Complete
Brons *et al.* (1980)	45	TAH	6	P	MPA	1	Partial
Gloor *et al* (1982)	28	TAH	14	P,A	MPA	2	Partial
O'Brien *et al* (1985)	35	STH,USO	2	P,A,L	MPA	2·5	Partial
Tsukamoto *et al* (1985)	30	TAH	3	P,V,L	17αHPC,MPA	2	Partial
Present report	32	TAH	10	P,A,L	MPA	7·5	Partial

TAH, Total abdominal hysterectomy; STH, subtotal hysterectomy; BSO, bilateral salpingo-oophorectomy, USO, unilateral salpingo-oophorectomy; P, pelvis, A, abdomen; V, vagina; B, bladder, L, lung; SE, spinal extradural, MPA, medroxyprogesterone acetate; 17αHPC, 17-alpha hydroxyprogesterone caproate; Meg.A, megestrol acetate.

further such case. The possibility of regression following simple hormonal treatment makes the recognition of these rare tumours a matter of clinical importance.

The tumour now known as low-grade endometrial stromal sarcoma has had numerous synonyms, including endolymphatic stromal myosis, uterine stromatosis and stromal endometriosis. Although some of these convey an impression of the particular propensity to vascular permeation, none conveys adequately the potential to recur, often after many years, and to metastasize widely. There is a danger of confusion with haemangiopericytoma. Jacobsen & Haram (1975) provide a succinct history of the terminology of these conditions.

High-grade tumours tend to occur in the postmenopausal age group. They are distinguished by their high mitotic rate and frequently bear more resemblance to the mesenchymal elements of mixed Mullerian sarcoma than to endometrial stroma. The relation between low-grade endometrial stromal sarcoma and the variants of high-grade endometrial stromal sarcoma has been the subject of debate (Evans 1982).

Our patient illustrates important features of low-grade endometrial stromal sarcoma, namely a tendency to late recurrence and metastasis, often after a disease-free interval of many years, and extreme sensitivity to hormonal manipulation rivalling that of any other malignant neoplasm.

Pellillo (1968) first reported the response of pulmonary metastases and pelvic recurrence of low-grade stromal sarcoma (proliferative stromatosis) to progestogen therapy. He tried this because of the known response of endometrial hyperplasia and carcinoma to this treatment, as well as ancillary observations on endometrial carcinoma in organ culture (Nordqvist 1964) and *in vivo* (Varga & Henriksen 1965) and the atrophic effect in the endometrium of normal subjects. Evidence for the progestogen sensitivity of the neoplastic endometrial stroma was strengthened by the findings of decidual change in a tumour removed at the menstrual phase of the cycle (Baggish & Woodruff 1972), another tumour removed after five days of progestogen therapy showing marked 'transformational swelling' by electron microscopy (Schmid 1974) and two patients with regression of presumed pulmonary metastases associated with progestogen therapy (Baggish & Woodruff 1972; Krumholz *et al.* 1973).

Since 1974 there have been five further reports of regression with progestogen administration of recurrent abdominal, pelvic or vaginal tumour and three additional patients with regression of pulmonary metastases. All these patients are detailed in Table 1.

It seems that the continued administration of the progestogen is important for the maintenance of the response. In our patient and in those described by Krumholz *et al.* (1973) and Tsukamoto *et al.* (1985), a clear relation between interruption of therapy and temporary recrudescence was noted. Notably we found no reports describing failure of high-dose progestogen therapy to effect a response in patients with low-grade endometrial stromal sarcoma. High-grade endometrial stromal sarcomas are said not to respond to progestogens (Tsukamoto *et al.* 1985).

The effect of oestrogen on stromal sarcomas is more problematical. The oncogenic effect of oestrogen on the endometrial stroma was suggested by the concurrence of endometrial stromal malignancy with ovarian theca cell tumours (Toker 1970); partial regression of intra-abdominal metastases of low-grade stromal sarcoma after oophorectomy has also been reported (Baggish & Woodruff 1972). Gloor (1978) in his review of treatment used in 78 patients reported in the literature has shown a higher rate of recurrence or metastasis after conservation of one or both ovaries, although in a series of 15 patients Norris & Taylor (1966) found no benefit of additional oophorectomy over total hysterectomy alone. In a trial of the anti-oestrogenic agent tamoxifen in advanced and recurrent uterine sarcomas of all types (Rome *et al.* 1986), the three endometrial stromal sarcomas showed no response; whether these were high- or low-grade tumours was, however, not specified. In our patient and in those reported by O'Brien *et al.* (1985) and Brons *et al.* (1980), tamoxifen had no obvious effect. The reason for removal of the adnexal structures is therefore the possibility of unrecognized microscopic extension of the tumour into these tissues rather than because an adverse effect of residual oestrogen production is proven.

Combination cytotoxic chemotherapy (Lehrner *et al.* 1979), examined critically (O'Brien *et al.* 1985), has no convincing clinically significant effect and radiotherapy does not yield consistently satisfactory results (Mastrota & Fenton 1964; Gloor *et al.* 1982).

We conclude from this and the other case reports that high-dose progestogen therapy is likely to give an excellent response in the treatment of low-grade endometrial stromal sarcoma, and should be considered in any recurrence or metastasis of this tumour.

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Development of an invasive macroprolactinoma: a possible consequence of prolonged oestrogen replacement. Case report

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Case report

After a late menarche at 16 years of age the patient had regular menses until her first pregnancy 5 years later. She miscarried at 14 weeks and was subsequently amenorrhoeic. Endocrinological assessment in 1968, at 23 years of age, revealed no abnormalities on clinical examination, though a vaginal smear suggested oestrogen deficiency. Plain skull radiographs showed a normal pituitary fossa. Prolactin assay was not available at that time and a detailed hormone profile was not obtained. A quadruplet pregnancy was induced by gonadotrophin therapy (Pergonal, Serono) in 1971 but amenorrhoea persisted after delivery. In 1973, after 7 years secondary amenorrhoea, she was treated with oestrogen replacement. Between 1973 and 1976 she received continuous oestrogen in the form of piperazine oestrone sulphate, 1·5 mg daily (Harmogen, Abbott Labs Ltd), but from 1976 until late 1984 this was administered cyclically, 3 weeks out of 4. Frequent moves around the country were necessary between 1973 and 1988 due to her husband's occupation. Endometrial biopsies in 1985 showed cystic hyperplasia with cytological atypia but no malignancy. Oestrogen therapy was therefore changed to a combined oestrogen and progestogen preparation to induce endometrial shedding (Prempak C, 0·625 μg conjugated oestrogens on days 1–28 and 150 μg norgestrol on days 17–28, Ayerst Labs Ltd) and annual currettage performed until endometrial histology returned to normal.

In July 1988, at age 43, she presented to our institution with a 6-month history of increasing lassitude, frontal headaches, intermittent vomiting and depression, but denied visual disturbance. She had stopped Prempak C in February 1988 and remained amenorrhoeic, but had no flushing or vaginal dryness. She had never noticed galactorrhoea. Physical examination revealed a pale, obese woman with diminished secondary sexual hair and no expressible galactorrhoea. Ocular movements, visual acuities and visual fields were normal. Fundoscopy revealed right optic disc swelling, without retinal haemorrhages, with less striking changes on the left.

Endocrine investigations showed grossly elevated serum prolactin (mean, 108 000 m-units/l), secondary hypogonadism, reduced growth hormone and partial ACTH deficiency (Table 1). Goldmann perimetry revealed slight bitemporal visual field loss. Computerized tomography (CT) with contrast enhancement showed a large invasive pituitary adenoma extending inferiorly into the sphenoid sinus and nasopharynx, laterally into cavernous sinuses and superiorly to the foramen of Monro producing obstructive hydrocephalus (Fig. 1).

After adrenocortical replacement therapy was established, bromocriptine was started and the dose gradually increased to 5 mg twice daily over a period of 1 week. This produced a dramatic fall in serum prolactin—90% reduction after the first tablet and to below 1000 m-units/l after 20 days of treatment (Fig. 2). No further headache or vomiting occurred and the right optic disc swell-

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Table 1. Serum hormone concentrations before and after 6 months of bromocriptine treatment

Hormone	Before	After	Normal range
Prolactin	112 000'	95	<420
(basal, 09.00 hours, m-units/l)	91 000	230	
	120 000		
17β-oestradiol (pmol/l)	<20	<20	80–250 (early follicular) (<200 postmenopausal)
LH (units/l)	2·9	2·5	2–8 (>15 postmenopausal)
FSH (units/l)	3·3	4·7	2–8 (>30 postmenopausal)
Free T4 (pmol/l)	11	11	8–26
TSH[a] (m-units/l)	3·5/18·2/15·4	2·7/13·2/11	<4 (basal)
Cortisol[b] (nmol/l)	440	390	>400
Growth hormone[c] (m-units/l)	<0·5	1·4	>20

[a] Values 0, 20 and 60 min after 200 μg TRH i.v.

[b] Peak after insulin hypoglycaemia; the second test was performed after steroid withdrawal for 5 days. There was subnormal urinary 17OH-corticosteroid excretion after metyrapone (250 mg orally, 2-hourly for 3 days) both before and after bromocriptine.

[c] Peak after insulin hypoglycaemia.

ing was reduced after 2 weeks and absent after 6 weeks of bromocriptine therapy. Repeat CT after 8 weeks of dopamine agonist treatment showed considerable tumour shrinkage and the ventricular system was much less distended (Fig. 1). At latest follow-up—after 6 months of bromocriptine—serum prolactin is within the normal range and the patient entirely well, but she remains amenorrhoeic with undetectable serum 17β-oestradiol; there has been no improvement in anterior pituitary function (Table 1) and CT shows a small amount of further shrinkage.

Discussion

It is likely that our patient had an undiagnosed microprolactinoma at first presentation in 1968, in the absence of available prolactin radioimmunoassay at that time, and we suggest that a major factor in the development of her invasive macroprolactinoma was the administration of oestrogens for 15 years, particularly as these were given continuously for the first 3 years and endometrial histology after 12 years showed marked oestrogen-associated changes.

Recent prospective studies of patients with microprolactinomas suggest that progression to a macroprolactinoma rarely occurs (March *et al.* 1981; von Werder *et al.* 1983; Martin *et al.* 1985) and the cause of such transition remains unknown. Serum prolactin increases during pregnancy in most women with microprolactinomas but this is transient and levels fall after delivery, occasionally to normal (Rjosk *et al.* 1982). Furthermore, clinically important tumour enlargement during pregnancy in such women is exceptionally rare (Nillius & Bergh 1984). Since the rise in serum prolactin during pregnancy in normal women and those with prolactinomas is believed to be oestrogen induced (Biswas & Rodeck 1976), is there evidence that exogenous oestrogen therapy can induce or promote growth of prolactinomas? The available data suggest that this can occur but that both the dose and duration of oestrogen therapy are critical, as we suggest for our patient.

Currently used oral contraceptives are not associated with an increased occurrence of prolactinoma (Wingrave *et al.* 1980) neither do they elevate serum prolactin above the normal range (Davis *et al.* 1984). Shy *et al.* (1983) found that women given the oral contraceptive for 'menstrual regulation' were at increased risk of prolactinoma, but this probably reflected underdiagnosis of pituitary tumour rather than an effect of the oral contraceptive. In contrast, Asscheman *et al.* (1988) reported significant hyperprolactinaemia (prolactin >1000 m-units/l) in 21% of male-to-female transsexuals treated with ethinyl oestradiol, 100 μg daily, or depot oestrogens. Serum prolactin fell after dose reduction but one of their patients, who self-administered excessive oestrogens, developed an autonomous prolactinoma (Gooren *et al.* 1988). In rats the administration of high doses of oestrogens induces lactotroph hyperplasia and subsequent adenomatous transformation (Wik-

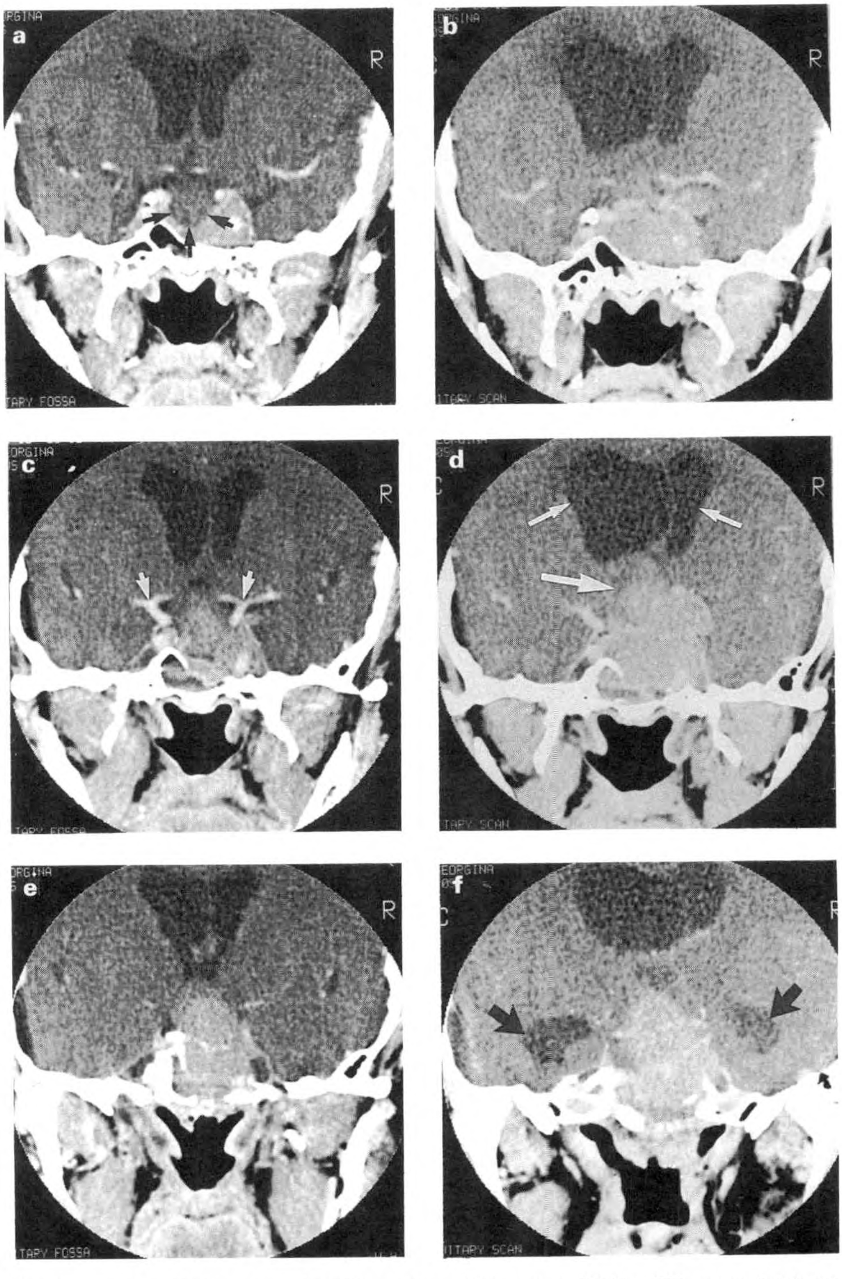

Fig. 1. Computerized tomography with contrast enhancement (Philips TX scanner). (a), (c) and (e) show coronal slices through anterior, middle and posterior regions of the tumour respectively, before, and (b) (d) and (f) after 8 weeks of bromocriptine. (b) Arrows indicate partial empty sella after bromocriptine. (c) Large arrow indicates upper part of suprasellar extension which has an inhomogeneous enhancement pattern. Small arrows indicate distended anterior horns of the lateral ventricles. (d) Internal carotid and middle cerebral arteries (arrows) clearly separate from tumour, and ventricular system less distended, after bromocriptine. (e) Arrows indicate distended inferior horns of the lateral ventricles, not visible after bromocriptine (f).

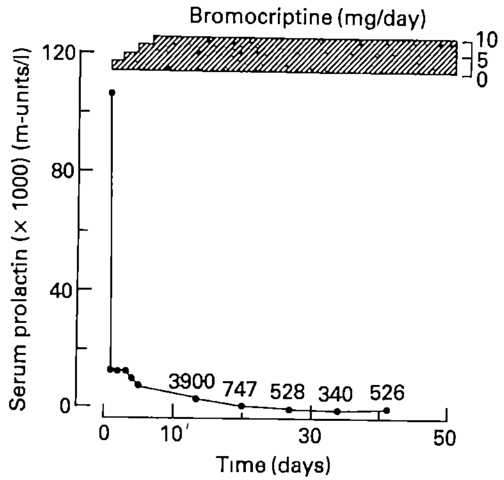

Fig. 2. Serum prolactin response to bromocriptine

lund & Gorski 1982). In women with prolactinomas there is considerable heterogeneity of serum prolactin responses to acute administration of oestrogens, suggesting variation in individual tumour susceptibility (White *et al.* 1981). This may be because only a proportion of prolactinomas possess cytosolic oestrogen receptors (Pichon *et al.* 1980). Moult *et al.* (1982) found no increase in serum prolactin or tumour size in eight women with bromocriptine-treated prolactinomas given a combined oral contraceptive containing 50 μg oestrogen for 6–19 months. There are a few case reports of oestrogen-induced growth of pre-existing macroprolactinomas (Landolt *et al.* 1984; Prior *et al.* 1987).

Piperazine oestrone sulphate treatment (1·5 mg dose) produces serum oestradiol levels comparable to those obtained in normal early follicular phase but serum oestrone and oestrone sulphate well in excess of mid-cycle levels (Anderson *et al.* 1978). There is evidence that previous exposure of a prolactinoma to oestrogens may enhance its response to dopaminergic inhibition (Valcavi *et al.* 1985) which may explain the exquisite bromocriptine sensitivity of the tumour in this report. It is imperative that women with untreated microprolactinomas who are given oestrogens, in whatever form, should receive careful assessment of serum prolactin and tumour radiology.

Our patient is of further interest in that she presented with obstructive hydrocephalus and papilloedema, the latter being a rare feature of pituitary tumour (Melen 1987), possibly prevented by pre-existing optic atrophy (Teasdale 1983). Of 274 patients with macroprolactinomas treated with dopamine agonists reviewed by Benker *et al.* (1986), none had this clinical presentation. Five of 16 'giant adenomas' (>40 mm diameter) described by Symon *et al.* (1979) had hydrocephalus and three died within 2 weeks of decompression via craniotomy. We are unaware of another reported case in whom medical treatment with bromocriptine successfully relieved obstructive hydrocephalus and papilloedema.

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Pulmonary oedema and salbutamol in preterm labour. Case report and literature review

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Case report

A 30-year-old primigravida with a twin pregnancy was transferred to Queen Charlotte's Maternity Hospital after spontaneous rupture of the membranes at 30 weeks gestation. She had no previous history of cardiovascular or other serious disease, and was taking no medication. However, she smoked 20 cigarettes a day and had continued to do so throughout pregnancy. Her arterial blood pressure was 120/70 mmHg on admission and her heart rate was 88 beats/min. Auscultation of lungs and heart revealed no abnormality, and the jugular venous pressure was not elevated.

Treatment initially comprised bed rest, fetal heart rate monitoring and oral phenoxymethylpenicillin for a beta-haemolytic streptococcal infection detected with a high vaginal swab.

Regular uterine contractions began 36 h after admission and an intravenous salbutamol (Ventolin) infusion was started to arrest uterine activity. During the next 48 h the rate of infusion was varied between 2 and 10 µg/min. Two intramuscular injections of 12 mg betamethasone (Betnesol) were administered to accelerate fetal lung maturation. Maternal heart rate varied between 105 and 120 beats/min during tocolytic therapy, and blood pressure between 120/60 and 150/70 mmHg. A positive fluid balance of 1200 ml was recorded after 48 h of treatment. At this time the patient complained of difficulty in breathing and was noted to have a respiratory rate of 20 breaths/min. The chest was clear on auscultation and blood pressure and heart rate were unchanged.

Shortly after this the rate of uterine contraction increased and the cervix was 4 cm dilated. The salbutamol infusion was therefore stopped and labour was allowed to progress. Epidural analgesia was requested and the duty anaesthetist examined the patient before inserting the catheter. The patient was now markedly tachypnoeic, with a respiratory rate of 25 breaths/min and central cyanosis. Her heart rate was 110 beats/min, arterial blood pressure was 130/60 mmHg, and early-inspiratory crepitations could be heard at both lung bases. Arterial oxygen tension ($Pa,_{O_2}$) was 6·04 kPa, carbon dioxide tension ($Pa,_{CO_2}$) was 3·0 kPa and the pH was 7·463. A chest X-ray and electrocardiogram were obtained; the former showed the typical features of pulmonary oedema while the latter was normal apart from a sinus tachycardia of 100/min.

Oxygen was administered (4 l/min by mask), while 40 mg frusemide (Lasix) and 5 mg diamorphine were given intravenously. A diuresis of 1500 ml occurred over a period of 3 h and the patient's sensation of breathlessness was relieved within 30 min. However, the $Pa,_{O_2}$ remained at the barely acceptable level of 10·16 kPa (saturation 96%), despite the administration of supplementary oxygen. Oxygen therapy was therefore continued throughout labour, and arterial oxygen saturation ($Sa,_{O_2}$) was monitored using the Ohmeda Biox 3700 pulse oximeter. $Sa,_{O_2}$ remained stable at 95–96% with supplementary oxygen, but dropped to 88–89% with the patient breathing air.

Following this treatment, and omitting the usual fluid preload, an epidural catheter was inserted at the L2/3 level A 10 ml dose of plain bupivacaine (Marcaine), 0·25%, was injected

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after a test dose. Sensory block was obtained with an upper level at T10, and arterial blood pressure remained stable. A further eight doses of 10 ml 0·25% bupivacain were administered during the course of labour, at approximately 1-h intervals. Analgesia and arterial blood pressure were both well maintained throughout.

Two hours after insertion of the epidural catheter, an intravenous infusion of oxytocin was started to augment uterine contraction. Within the next 10 h urine output dropped to 15 ml/h, but increased in response to a further intravenous dose of 20 mg frusemide.

Approximately 15 h after the onset of labour the first twin began to exhibit signs of fetal distress. The cervix was found to be fully dilated and both twins were born by forceps, following the administration of 15 ml of 2% lignocaine with 75 µg of adrenaline (1:200 000) via the epidural catheter. A good sensory block was obtained between T8 and S5, providing excellent analgesia during delivery. No fluid preload was given, but 60 mg of ephedrine were diluted in 500 ml of Hartmann's solution and kept at hand in case of hypotension. In the event, systolic blood pressure remained above 100 mmHg at all times and the ephedrine was not required.

The twins had 5-min Apgar scores of 10 and 9 respectively and weighed 1·36 and 1·7 kg. The second twin subsequently developed the infantile respiratory distress syndrome and required artificial ventilation for a period of 3 days. Both were doing well 1 week after birth.

One hour after delivery the mother felt well and no added sounds could be heard on auscultating the chest. However, with the patient breathing air her Pa,o_2 remained low at 7·23 kPa (Sa,o_2 90%), despite a negative fluid balance of 2 litres over 24 h. Nine hours after delivery the Sa,o_2 was 92% with the patient breathing air, and the supplementary oxygen was discontinued. She remained well and was discharged to her own hospital 1 week later.

Discussion

Pulmonary oedema has been reported on a number of occasions following the use of beta-sympathomimetic drugs to arrest premature labour. Despite a reported frequency of 5% for this potentially serious complication (Wagner *et al.* 1981), there appears to be limited understanding of the need for cardiovascular monitoring of the mother.

Complications associated with the use of beta-sympathomimetic agents in premature labour were reviewed by Benedetti (1983). Pulmonary oedema, cardiac arrhythmias, hypotension, hyperglycaemia and hypokalaemia have all been reported. Pulmonary oedema is an adverse reaction unique to the parturient patient, and has been reported with all the commonly used tocolytic agents (Elliott *et al.* 1978; Davies & Robertson 1980; Ravindran *et al.* 1980). The pathogenesis of the condition is poorly understood, and early papers blamed a combination of tachycardia and fluid overload causing left ventricular failure (Davies & Robertson 1980). However, studies using pulmonary artery catheterization have failed to detect evidence of cardiac failure (Wheeler *et al.* 1981; MacLennan *et al.* 1985). Wagner *et al.* (1981) used M-mode echocardiography to investigate the effects of terbutaline (Bricanyl) on left ventricular size and function in women undergoing treatment for preterm labour. They concluded that in these patients terbutaline was a potent inotropic and chronotropic agent and that the occasional pulmonary oedema was probably not due to cardiac failure. In the non-pregnant patient, sulbutamol actually improves the signs and symptoms of chronic cardiac failure (Bourdillon *et al.* 1980).

Alternative mechanisms are an increase in pulmonary capillary permeability, or a decrease in pulmonary lymphatic activity. During pregnancy, pulmonary vascular pressures alter little, but the hydraulic conductivity of the alveolar-capillary membrane increases and plasma oncotic pressure decreases (MacLennan 1986). These changes would be expected to cause an increase in total lung water during pregnancy, and this has been shown to be the case (MacLennan *et al.* 1987). Beta-sympathomimetic agents appear to act by increasing the permeability of the alveolar–capillary barrier, and in one report of fatal pulmonary oedema precipitated by ritodrine, total lung water was found to be five times the normal value (MacLennan *et al.* 1985).

Fluid overload also appears to play a part in the development of pulmonary oedema in these patients. Overload may be 'physiological', as in multiple pregnancies, or iatrogenic. Fluid retention due to corticosteroids may be important, but evidence is lacking. The corticosteroids most commonly used in preterm labour are betamethasone and dexamethasone, neither of which has significant mineralocorticoid activity.

Oxytocic agents, if used during the course of labour, may also play a part. Oxytocin is known to promote fluid retention by an antidiuretic hormone-like action.

Management

The avoidance of potentially serious complications of tocolytic therapy requires careful patient monitoring and an awareness of these complications.

Mothers at special risk include those with hypertension, diabetes, coronary and valvular heart disease, and obstructive cardiomyopathy. Additional risk factors warranting especially careful monitoring include multiple pregnancy, amniotic fluid infection and possibly smoking which has not been considered a risk factor, but is known to increase the permeability of the alveolar–capillary barrier (Jones *et al.* 1982) and may have been an important factor in our patient.

Before treatment with a beta-sympathomimetic agent is started, every patient should have an electrocardiogram and blood glucose measurement. Heart rate and blood pressure should be recorded at least once hourly, and in high-risk pregnancies the electrocardiogram should be displayed continuously on a bedside monitor. Regular auscultation of the lung bases may be advisable, but appears to be a poor method of detecting clinically significant pulmonary oedema. Continuous monitoring of arterial oxygen saturation is a more sensitive index. Taylor & Whitwam (1986) have recommended that effective warning of impending hypoxaemia is best achieved by setting the oximeter alarm at an Sa,o_2 of 94%, corresponding to an arterial oxygen tension of 10 kPa. Above this level there would appear to be little risk to mother or fetus.

The importance of restricting fluid intake has been stressed in a number of reports. A detailed and accurate record must be kept of fluid input, both oral and intravenous, and of urine output.

If the patient becomes dyspnoeic, arterial blood gases should be measured, a chest radiograph obtained, and tocolytic therapy may have to be discontinued. If indicated, oxygen and diuretics should be given. More severe cases may require positive pressure ventilation, direct arterial pressure monitoring and pulmonary artery catheterization.

Management of anaesthesia

The anaesthetic management of these patients has been the subject of relatively few reports. Ravindran *et al.* (1980) described three patients who required general anaesthesia after receiving intravenous terbutaline, two for cervical cerclage and one for caesarean section. All three patients experienced marked tachycardia during surgery, and in one this was associated with hypotension. Multifocal ventricular extrasystoles were reported in one patient and were associated with the use of halothane (Fluothane).

Marks & De Chazal (1984) reported a patient in whom tachycardia and pulmonary oedema, caused by intravenous ritodrine (Yutopar), were improved by the use of epidural analgesia during labour, attributed to a reduction in venous return to the heart. Subsequently the patient was delivered by caesarean section under epidural analgesia with no adverse effects on the cardiovascular system.

Shin & Kim (1986) compared general anaesthesia with epidural analgesia in groups of women delivered by caesarean section after uncomplicated ritodrine therapy. Three patients in the epidural group developed hypotension whereas none in the general anaesthesia group developed any complication. Two of the three patients who developed hypotension had received an epidural injection of local anaesthesia within 30 min of discontinuing the ritodrine infusion.

The risks of general anaesthesia in the third trimester of pregnancy are well known and include aspiration of gastric contents, failed intubation, maternal awareness and depression of the fetus by anaesthetic agents. Added to these risks are those of myocardial depression and cardiac arrhythmias when volatile anaesthetics are used, risks which may be exaggerated by the use of beta-2-sympathomimetic agents.

Epidural analgesia offers many advantages, including avoidance of arrhythmias, and by reducing peripheral vascular resistance and venous return may actually improve pulmonary oedema. There appears to be an increased potential for hypotension, especially when epidural analgesia is instituted within 30 min of stopping tocolytic treatment, but this may be obviated by delaying epidural catheterization. Hypotension can also be prevented by using an incremental dose technique to establish the block, and by infusing ephedrine as appropriate. It is obviously important to avoid large fluid preloads in a patient who may already be overloaded.

Our experience suggests that epidural analgesia is the technique of choice for pain relief in labour following the use of beta-2-sympathomimetic drugs, and for operative delivery if this is necessary. A careful examination of the heart and lungs should be made beforehand, and we would recommend continuous monitoring, throughout labour, of the maternal electrocardiogram and arterial oxygen saturation. Women with multiple pregnancy or infected uterine contents are at special risk of developing pulmonary oedema if treated with tocolytic drugs, and need careful monitoring. The importance of keeping an accurate record of fluid intake and output cannot be stressed too highly, especially if oxytocin is used during labour.

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SHORT COMMUNICATIONS

Discordant umbilical artery flow velocity waveforms and pregnancy outcome

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Umbilical artery flow velocity waveforms (FVWs) are easily obtained using Doppler ultrasound. Almost all umbilical cords contain two arteries, and FVWs are obtained at random from one or other artery during Doppler examination. Reproducibility studies suggest that FVWs from the two arteries in an umbilical cord are usually very similar (Reuwer *et al.* 1984; Murills *et al.* 1987). However, different umbilical artery FVWs have been reported in one patient, and after delivery a large placental infarct supplied by only one of the arteries was discovered (Trudinger & Cook 1988).

During a research study of umbilical artery FVWs in high-risk pregnancies, we observed seven singleton fetuses with two distinctly different (discordant) umbilical artery FVWs. Three patients had severe pre-eclampsia, one had chronic renal hypertension, one had systemic lupus erythematosus with pre-eclampsia and two fetuses were very light for gestational age.

From clinical identification as 'high-risk' each patient had serial Doppler studies at intervals ranging from 1 to 21 days. The Doppler data were not revealed to the clinicians. All observations were made with the patient semi-recumbent. A range-gated pulsed Doppler MkV Duplex mechanical sector scanner (Advanced Technology Laboratories) with a 3 MHz transducer was used. The sample volume was placed within the umbilical artery using real-time imaging before switching to the Doppler mode. After on-line Fast Fourier Transform spectral analysis, returning Doppler-shifted signals were displayed and a hard copy recording made. FVWs were only recorded during fetal apnoea. The pulsatility index (PI) (Gosling & King 1975) was used to quantify FVW characteristics.

Discordant umbilical artery FVWs were diagnosed only if two distinctly different artery FVWs were consistently detected at different sites along the cord at optimum angles of insonation. The difference between the two FVWs was always visually apparent and the diastolic flow characteristics were different (Fig. 1) in all except one case. All PI values were greater than the normal range (mean + 2 SD) for gestational age, except for one artery in one fetus. The difference in PI between the discordant arteries ranged from 0·46 to 2·67. The time between first observation of discordant arteries and delivery was 1–14 days, and between the immediately previous observation and delivery 2–28 days.

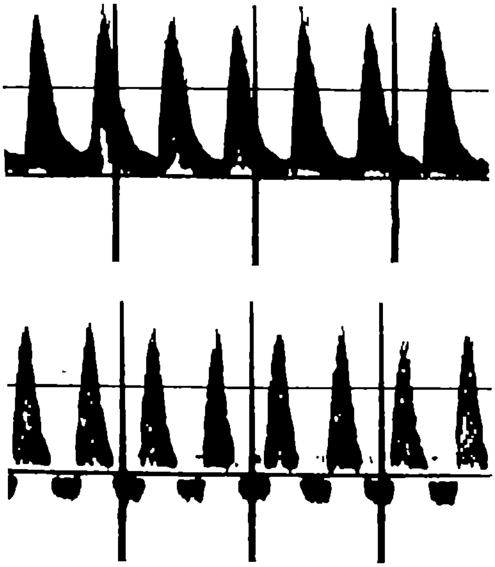

Fig. 1. Discordant umbilical artery FVW from one fetus at 29 weeks gestation, upper showing reduced end diastolic flow velocities (PI 1·73), lower showing reversal of end diastolic flow velocities (PI 4·4). A 1105 g male infant was born by caesarean section at 31 weeks gestation because of abnormal cardiotocography (flat tracing with decelerations). The placenta weighed 250 g and approximately half was infarcted.

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Six fetuses developed abnormal fetal heart rate patterns either antenatally or during labour, necessitating urgent delivery. All were born by caesarean section between 30 and 34 weeks gestation, and all were ≤3rd centile of weight for gestation (Gairdner & Person 1971). Six placentas had extensive infarcts often involving 50% of their total volume; the seventh had an old retroplacental clot which had caused partial separation. Six infants survived and one died aged 6 weeks from cardiomyopathy.

Discussion

The umbilical arteries are joined by a wide transverse anastomosis (Hyrtl's anastomosis) just before entering the placenta (Boyd & Hamilton 1970). Presumably this equalizes pressure and flow so that FVWs from the two umbilical arteries are normally indistinguishable.

Discordant umbilical artery FVWs in a single cord suggest that vascular resistance is considerably higher in one portion of the placenta than in the other. This could be explained by the extensive unevenly distributed areas of placental infarction found in six of our patients and by the retroplacental clot in the seventh. Large areas of infarction (involving more than 10% of total placental volume) are found almost exclusively with pre-eclampsia and are due to restricted uteroplacental blood flow (Fox 1986). Abnormal umbilical artery FVWs in association with placental abruption have been reported (Morrow & Knox Ritchie 1988; Defoort *et al.* 1989).

Discordant umbilical artery FVWs in an individual fetus are unusual and suggest significant placental damage. They may persist for some time and are not in themselves an indication for urgent delivery, but such fetuses are likely to be compromised and should be monitored very closely.

Acknowledgments

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Cord serum alpha-fetoprotein and maternal insulin-dependent diabetes mellitus

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Maternal serum alpha-fetoprotein (AFP) levels in the second trimester of pregnancy are lower in pregnancies associated with maternal insulin-dependent diabetes mellitus than in those without diabetes (Wald *et al.* 1979; Milunsky *et al.* 1982; Reece *et al.* 1987; Greene *et al.* 1988; Cuckle & Wald 1989). On the basis of published data on a total of nearly 800 diabetic pregnancies, the average AFP level is 0·77 multiples of the normal median level for the appropriate ges-

Table 1. Cord serum alpha-fetoprotein (AFP) levels in 26 pregnancies associated with maternal insulin-dependent diabetes and 130 unaffected matched controls.

		AFP (iu/l)						
	Gestation of case at delivery		Controls*					
Case no.	(weeks + days)	Case	1	2	3	4	5	Case/control (3)
1	33 + 1	58	86	95	309	390	500	0·19
2	35 + 1	325	139	141	146	246	276	2·23
3	35 + 4	86	107	173	175	234	272	0·49
4	35 + 5	217	89	112	144	145	229	1·51
5	36 + 0	211	72	99	107	201	500	1·97
6	36 + 2	251	131	139	152	161	175	1·65
7	36 + 4	339	87	100	139	272	631	2·44
8	36 + 4	112	51	72	79	94	158	1·42
9	36 + 4	199	83	92	102	118	182	1·95
10	37 + 0	257	92	101	113	120	138	2·27
11	37 + 1	214	89	126	133	141	363	1·61
12	37 + 2	105	67	88	111	123	196	0·95
13	37 + 2	248	53	107	118	251	348	2·10
14	37 + 2	111	24	76	84	123	345	1·32
15	37 + 2	153	33	44	94	163	271	1·63
16	37 + 4	274	91	115	141	191	226	1·94
17	37 + 6	128	48	125	160	161	188	0·80
18	37 + 6	76	45	64	104	135	154	0·73
19	37 + 6	289	55	117	128	144	160	2·26
20	38 + 2	59	35	35	64	66	179	0·92
21	38 + 4	46	25	60	60	68	176	0·77
22	38 + 4	285	73	104	147	158	163	1·94
23	38 + 5	86	55	81	98	101	122	0·88
24	38 + 6	129	72	118	132	158	170	0·98
25	39 + 1	146	33	39	57	129	156	2·56
26	42 + 2	76	38	47	56	66	78	1·36
							Median	1·56

* Arranged in rank order, 1 is the lowest, and 5 the highest value

tational age (Cuckle & Wald 1989). Since maternal serum levels increase, on average, by about 17% a week at this time in pregnancy, the low AFP levels could be explained by a 1–2 week delay in the development of the fetal liver—the principal source of AFP after the first trimester. In the third trimester fetal serum AFP levels decline so that if there was developmental delay umbilical cord serum AFP levels would be raised. This seems to be the case since in 40 infants born to mothers with insulin-dependent diabetes mellitus, cord serum AFP levels were, on average, higher than the expected level for infants born at the same gestational age, based on values in 45 infants born to unaffected mothers, and were similar to the expected levels for infants born to unaffected mothers 1–2 weeks earlier (Norgaard-Pedersen & Klebe 1974). To explore the matter further we measured the concentration of AFP in another series of umbilical cord sera collected from 26 newborn infants whose mothers had insulin-dependent diabetes and from 130 matched controls.

Methods and results

As part of a large epidemiological study of pregnancy, cord blood was routinely collected from infants born between June 1973 and March 1978 at the John Radcliffe Hospital, Oxford and the serum stored at −40°C. We retrieved the cord sera from all 26 infants born in this period to women with diabetes (cases) together with the sera from five controls for each case. Case and control pregnancies (all singleton) were matched for gestational age at delivery (within 2 days), estimated from the first day of the last menstrual period, and the duration of storage of the serum samples (within a year except for five sets in which for at most two of the controls the difference was up to 4 years). AFP was measured by radioimmunoassay without knowledge of whether the samples were from cases or controls. Values were ranked within each matched set and a non-parametric statistical test was used to compare differences between cases and controls (Kwa *et al.* 1981) using χ_1^2 calculated as $(R-M)^2/V$ where R is the average rank of the cases, and M and V are the average mean and variance of the ranks in each matched set.

Table 1 shows the individual AFP results. The AFP concentration is given in iu/l and the value for each case is also expressed as a multiple of the median (MoM) value for the five controls. The AFP concentration in the cases was statistically significantly higher than in the controls ($\chi_1^2 = 5{\cdot}3$, $P<0{\cdot}01$, one-tail test) with a median value of 1·56 MoM. A regression analysis in the controls showed that the AFP concentration declined, on average, by 3·4% a day at this time in pregnancy. The levels in cases were typical of the controls 13 days earlier in pregnancy ($1{\cdot}56 = 0{\cdot}966^{-13}$) with a 95% confidence interval of 7–19 days.

Conclusion

This result confirms the finding by Norgaard-Pedersen & Klebe (1974). We know that AFP levels in second trimester maternal serum, which increase with increasing gestation, are relatively low, and AFP levels in third trimester cord serum, which decrease with increasing gestation, are relatively high in diabetic pregnancies. Both observations can be explained by diabetic women having a 1 to 2 week delay in the development of the fetal liver. It would appear that the explanation applies more to the liver than to other measures of fetal development. For example, the crown–rump length was reduced by the equivalent of only 5 days growth, on average, in 99 diabetic pregnancies (Pedersen & Molsted-Pederson 1981) and the biparietal diameter was reduced by 1·5 days, on average, in 57 diabetic pregnancies (Wald *et al.* 1981). A third study found no reduction of crown–rump length in 20 diabetic pregnancies (Cousins *et al.* 1988).

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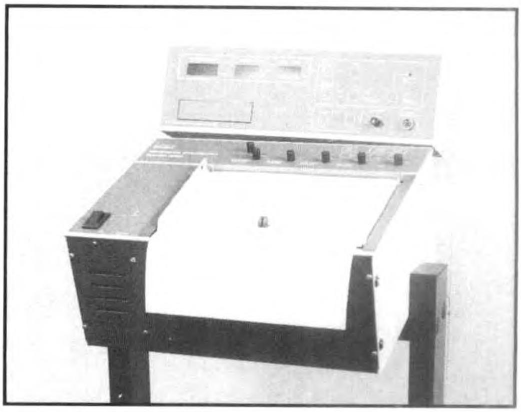

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CORRESPONDENCE

Evidence of redistribution of cardiac output in asymmetrical growth retardation

Dear Sir,

Assessment of reproducibility for any new technique is important. We therefore read with interest the conclusion of Dr Al-Ghazali and colleagues [*Br J Obstet Gynaecol* (1989) **96**, 697–704] that 'the reproducibility for both diameter and velocity measurements indicates that quantitation of blood flow across the ascending aorta and pulmonary artery by cross-sectional Doppler echocardiography can be sufficiently accurate for comparison of results'.

The study of reproducibility upon which this statement is based does not assess all the possible sources of error so that there may be underestimation of the effect of measurement variation. The study of inter-observer reproducibility addresses only the measurement of diameters from pre-selected images ignoring errors associated with image selection. There is no study of the inter-observer reproducibility of Doppler velocity measurements. The study of intra-observer reproducibility looks at both diameter and velocity measurements but the time interval (10–15 min) is short enough for the operator to remember the first measurement occasion while making the second measurement. Thus both inter- and intra-observer measurement error may be underestimated.

The calculation of volume flow will involve an accumulation of errors from diameter and velocity measurements. The error from the diameter measurement will be approximately doubled because diameter is squared in the flow formula. The authors recommend that an error of vessel diameter exceedings 0·5 mm should be avoided as this would limit the effect on flow to 10–15%. The is suggested despite the 0·5 mm being less than the axial resolution quoted for their equipment. In addition, they say that changes in blood flow velocity of 5–10% can be detected. If these errors are added then the effect on volume flow will be 15–25%. It is not therefore clear how the authors can comment that 'the variability of flow due to reproducibility errors should be limited to 10–15%'.

Reproducibility of diameter and velocity measurements cannot be assumed to imply reproducibility of volume flow. To ascertain this, a study looking directly at the reproducibility of volume flow estimations rather than the component parts is required. Until this is done there must remain doubt over the reproducibility of volume flow measurements in the fetal heart.

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Reference

Al-Ghazali W., Chita S. K., Chapman M. G. & Allan L. D. (1989) Evidence of redistribution of cardiac output in asymmetrical growth retardation *Br J Obstet Gynaecol* **96**, 697-704.

Authors' reply

Dear Sir,

Thank you for the comments on our paper. We remain convinced that our observations are sufficiently accurate for the comparison of results.

Blood flow is quantified from the formula

$$Q=\text{mean } V\times D/2\times\pi/\cos \text{ angle}.$$

Only angles of less than 20° were accepted where the cosine of the angle of insonation approaches unity.

The errors associated with image selection in inter-observer reproducibility were minimized by our use of the mean of four images selected for the clarity of the image of the walls of the arteries during diastole. The variation for two observers selecting their own images from a videotape recording was less than 0·3 mm in practice despite this being less than the quoted axial resolution of our machine.

We, and others, have examined the reproducibility of Doppler velocity measurements. This forms part of Dr Al-Ghazali's thesis. It would probably have been more accurate for us to have stated 'that the variability of flow due to reproducibility errors should be limited to 10–20%' but the detected difference in volume flow between the normal and the growth-retarded fetuses was greater than this.

We do not see why the variation in volume flow should be greater than the sum of the variation in the component parts.

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(1) Commentary. The obstetric vacuum extractor is the instrument of first choice for operative vaginal delivery.
(2) North Staffordshire/Wigan assisted delivery trial
(3) A multicentre randomized trial comparing delivery with a silicone rubber cup and rigid metal vacuum extractor cups.

Dear Sir,

I must dispute the uncritical enthusiasm for the use of the silastic vacuum extractor cup expressed by Chalmers & Chalmers, Johanson *et al.* and Cohn *et al.* [*Br J Obstet Gynaecol* (1989) **96,** 505–506, 537–544 and 545–551. The authors concerned are of the opinion that all labour wards should consider introducing this device, as superior to the obstetric forceps, although the results presented for the instrument are relatively poor. Johanson *et al.* report a 73% success rate using a pressure of −0·6 to −0·8 bar, whilst Cohn *et al.* using no more than 500 mmHg (equivalent to −0·65 bar), report a success rate of 81%. It has to be recognized that if a new design of forceps emerged with a successful delivery rate of 73% it would never enter obstetric use.

The poor success rate with the Kobayashi vacuum extractor is confirmed by other authors: Dell *et al.* (1985) report a 72% success rate in outlet cases; Berkus *et al.* (1986) 65% in suitable cases; and Hastie & MacLean (1986) 46% in mid-cavity rotational operative deliveries.

My preference is for the Bird design of metal cup vacuum extractor, which, although it requires more operator expertise in correct application, leads to a much better success rate both for rotation and delivery. Bird (1982) reported success rates of 99·5% and 99·1% in two series; Orhue (1984) reported 97%; and Ngan *et al.* (1986) 97·7%. Vacca *et al.* (1983), reporting the Portsmouth operative delivery trial, credited the Bird cup with an 87·5% success rate, but it must be recognized that many of the obstetricians involved had limited experience of vacuum extraction and the procedure tended to be left to junior obstetricians.

My personal experience of vacuum extraction within the UK (mainly Bird anterior cup) extends to 190 cases in three years, with an overall success rate of 91%. This includes a consecutive series of 88 cephalic, singleton term deliveries at Kings Mill Hospital, Mansfield, in 1986–7. During this period, the major reasons for failure were use of the Kobayashi cup on labour wards that had introduced this new design, failure of the vacuum system (hand pump), fetal macrosomia, and occipito posterior position.

The use of the silastic cup is associated with certain very definite problems. (i) The tendency for the edge of the cup to inroll under traction, with consequent loss of suction, which can be shown by establishing a vacuum to the cup whilst it is applied to a flat surface (see also Duchon *et al.* 1988). (ii) The inability of the cup to act to increase flexion, and hence rotation and ease of delivery with a deflexed head. (iii) The lack of function of the obstetrician's left hand, which in metal cup procedures adds to the 'feel' of the operation by holding the cup on to the fetal head. (iv) The encouragement of a 'suck it and see' mentality in the junior obstetrician, where this large cup (65 mm) is simply applied to the leading part of the fetal head, without the diligent attention to determination of position essential to sound obstetric practice.

Cohn *et al.* also make unsubstantiated points in favour of the silastic cup, compared to the metal cup. Their quoted increased speed of assembly, compared to the Bird cup system, is in my opinion marginal. Likewise, the vacuum can be established just as quickly and safely with metal cups as silastic cups (Bird 1982; Svenningsen 1987). Their statement that metal cups sometimes 'fly off' suggests poor technique, as this should never happen, and the claim that the silastic cup is less likely to entrap and lacerate the vaginal epithelium is unproven, even by their own study.

In summary, the published studies by Johanson *et al.* and Cohn *et al.* have failed to show that the silastic vacuum extractor has significant advantages over the Bird metal cup. It must be agreed that the silastic cup is equally as safe for the mother as the metal cup, but it has not been shown to be safer for the fetus, and is significantly less effective at achieving vaginal delivery. The Bird cup lies unused in the cupboards of many British labour wards, and its use should be enouraged before funds are used to purchase the Kobayashi device.

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Svenningsen L. (1987) Birth progression and traction forces developed under vacuum extraction after slow or rapid application of suction. *Eur J Obstet Gynaecol Reprod Biol* **26**, 105-112.

Vacca A., Grant A., Wyatt G. & Chalmers I. (1983) Portsmouth operative delivery trial: A comparison of vacuum extraction and forceps delivery. *Br J Obstet Gynaecol* **90**, 1107-1112.

Dear Sir,

I read with surprise the commentary by Chalmers & Chalmers on 'The obstetric vacuum extractor is the instrument of first choice for operative vaginal delivery' [*Br J Obstet Gynaecol* (1989) **96**, 505–506] for my interpretation of the literature is different from theirs.

The silicone vacuum extractor is widely used in American teaching hospitals. Our house officers use the silastic cup four to five times as frequently as they do forceps. Almost in vain, I have attempted to emphasize the value of forceps for the very reason noted in the same issue of the journal by Johanson *et al.* that forceps were 90% successful in their study, as compared to 73% for the silicone cup. I emphasize in my teaching that when the cup has failed, this is not the time to fumble with attempting to apply the forceps; the skilful use of the forceps requires their frequent use. By contrast, in 13 years of teaching the Kobayashi silicone cup application, I have never seen a calm novice unable to apply the cup satisfactorily in a cooperative patient.

Just as the newer Kobayashi cup is easier to apply and less traumatic than the Malmstrom cup, so likewise are the newer divergent forceps when compared to the Kielland forceps (Goodlin 1986). I have seen a near fatal fetal haemorrhage after scalp sampling and use of the vacuum cup. In other words, despite meeting the strict requirements of a randomized controlled trial, I do not agree that the study by Johanson *et al.* was an accurate comparison of the two techniques.

But most of all, I do not understand the authors apparent lack of concern for pain relief. In my experience, most multigravida delivered spontaneously over an intact perineum still appreciate a good pudendal block. I suppose all pain relief could be eliminated in normal parturients and large sums of money and time be saved, but that goal is not why most of us chose obstetrics.

To suggest that only hypotheses tested by randomized controlled trials are valid in my view replaces the investigating surgeon with a statistician. Surely there is more to studying and teaching obstetrics than whether we use 'a consecutive series of opaque envelopes prepared at the National Perinatal Epidemiology Unit' (Johansen *et al.* 1989).

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Johanson R., Pusey J., Livera N & Jones P. (1989) North Staffordshire/Wigan assisted delivery trial. *Br J Obstet Gynaecol* **96**, 537-544

Dear Sir,
The main issue raised by the 'North Staffordshire/Wigan assisted delivery trial' reported by Johansen *et al.* [*Br J Obstet Gynaecol* (1989) **96**, 537–544] is adequacy of training and supervision of Senior house officers carrying out instrumental deliveries. In 41 of 264 assisted deliveries a switch to alternative instruments or caesarean section was necessary. That represents a true failure rate of 11·4% for the ventouse and a 6·8% failure rate for forceps (including 'true' failures and failed applications). Both of these are extremely high rates and suggest either operator inexperience or inappropriate patient selection for delivery despite the statement that those involved were experienced.

Furthermore it seems that only two deliveries were by a senior registrar and one by a consultant. A failed instrumental delivery is usually an indication for senior assistance which is only documented as having occurred in three out of 41 failed instrumental deliveries. The above fears are compounded by the complication rates, examples of which are the 16% third-degree tear rate with forceps and 8% rate of tears into the fornices.

Contrary to the assessment by Drs J. A. and I. Chalmers in the same issue of the journal, we find *no objective* evidence in this paper which proves the general superiority of the ventouse over forceps in any variable independent of experience. It is acknowledged that the ventouse is to be preferred for some cases but skill with the safe use of forceps is necessary for other situations such as the delivery of the after-coming head and in a face presentation.

Neither instrument is dangerous in itself but inexpert or inappropriate usage can make them so. Surely our aim must be to supervise and train junior staff until they have mastered the strengths and weaknesses of, and relative indications for, all techniques for the assisted delivery of the parturient in the second stage of labour.

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Authors' replies

Dear Sir,
We thank you for the opportunity to comment on the points made in the letters by Greenwood and Pardey *et al.*

Our enthusiasm for the silastic vacuum extractor cup is not uncritical, as suggested by Dr Greenwood. He may have missed the conclusion of our report, which specifically highlighted the limitations of the 'Silc-cup'. We agree there is a place for the metal cup and this is being explored in a further randomized study at Stoke.

The reasons we felt that the 'Silc-cup' deserved investigation were first our initial favourable experience with it and second the studies by Hammarstrom *et al.* (1986) and Dell *et al.* (1985). We feel that the effects of the instrument on fetal and maternal trauma are of greater importance than the satisfaction of the operator based on other criteria.

There is no loss of function of the left hand while using the 'Silc-cup' as suggested by Dr Greenwood. The manufacturers recommend that this is used to ensure descent of head and not just scalp during traction. With any operative delivery, diligent attention to determine position is mandatory; operators with a 'suck it and see' mentality should not practise obstetrics.

With respect to the comments of Pardey *et al.*, when the delivery was conducted by a senior house officer this was supervised by a more senior obstetrician. There is active participation by the consultants and one senior registrar on the delivery suites at the North Staffordshire Maternity Hospital. One strength of the trial is that the study was conducted at two district general hospitals, and a district general hospital is where most women are delivered.

The decision to attempt a vaginal delivery was incorrect in only three of 264 deliveries. Third-degree tear rates of 12% with forceps and 5% with the ventouse (not 16% and 6% as quoted by Pardey *et al.*) are unacceptable, and illustrate the need to find ways to reduce the maternal trauma. Pardey *et al.* suggest this is a result of inexperience. In the Portsmouth trial (Vacca *et al.* 1983) 16% of forceps deliveries and 6% of the ventouse deliveries had third-degree tears. The forceps deliveries were more likely to have been performed by an operator with considerable experience compared with the ventouse deliveries. As the Editorial (1984) in the *Lancet* put it, 'think what the results would have been like if it had been the other way round'.

If an operative delivery is required, and if the 'Silc-cup' is likely to be successful, it is probably the least traumatic instrument for mother and baby. There are, however, occasions when the metal cup and forceps are required and expertise should be acquired with all instruments.

We agree that the ventouse should be taken out of the cupboards.

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Dear Sir,

Thank you for offering us the opportunity to comment on the letters you have received in response to our suggestion that the vacuum extractor should be regarded as the instrument of first choice for assisted vaginal delivery. Perhaps we can be allowed to reiterate the relevant evidence using different words to make our point. Obstetricians who select forceps (rather than some form of vacuum extractor) as the instrument with which to embark on an assisted vaginal delivery will more frequently fail to avoid traumatizing the mother during delivery. This pattern has now been observed in each of the four available unbiased comparisons of the two policies (Lasbrey *et al.* 1964; Dell *et al.* 1985; Vacca *et al.* 1983; Johanson *et al.* 1989). It was observed across all grades of obstetric staff in the only study in which this question was examined (Vacca *et al.* 1983). In the only trial in which the views of women were sought, women allocated to forceps delivery were more likely than those allocated to vacuum extraction to report that they had experienced moderate or severe pain during and after delivery (Garcia *et al.* 1985), and this difference was observed in spite of the fact that women allocated to forceps were more likely to have received either a pudendal or an epidural block (Vacca *et al.* 1983). Those who wish to consider a more extended presentation and discussion of the existing evidence are referred to Vacca & Keirse (1989).

Obstetricians and others who disagree with our conclusions must produce proper evidence to overturn them, not unsubstantiated opinions such as those contributed by your correspondents. We reiterate our contention that the evidence currently available suggests that, in places where forceps continue to be used as the instrument of first choice, a substantial proportion of women who require instrumental vaginal delivery are sustaining unnecessary trauma and experiencing avoidable discomfort. As we also wrote in our Commentary, those who believe that some important advantage of retaining forceps as the instrument of first choice remains undetected should conduct the unbiased comparisons required to test their as yet unsupported hypotheses.

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Dear Sir,

Dr Greenwood fails to comprehend the robust nature of data obtained from carefully designed prospective randomized controlled trials such as ours.

There was no significant difference between the success rate for assisted vaginal delivery in our series (81% Silc-cup, 84% metal cup delivery with intended instrument). The implication of this is that an enthusiast for vacuum delivery such as Dr Greenwood might obtain a success rate close to the 91% he obtains with the metal cup, were he to give the Silc-cup a fair chance in a similar uncontrolled personal case series.

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Aggressive angio-myxoma of the vulva

Dear Sir,

A young girl of 22 years came under my care recently with a vulval swelling which I believed was a Bartholin's cyst. After three operations a diagnosis has now been made of an aggressive angio-myxoma. The literature is mostly confined to pathology journals and suggests that it frequently recurs and is often associated with very major surgery. I should like to use the columns of this journal to gain advice on management. May I ask any clinician with experience of this condition to write to me so that I may correspond directly?

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BOOK REVIEW

Doppler Ultrasound: Physics, Instrumentation and Clinical Applications by D. H. Evans, W. N. McDicken, R. Skidmore & J. P. Woodcock. John Wiley & Sons, Chichester, New York, 297 pages with figures and tables, £47.50

During the last decade there has been increasing interest in the possible applications of Doppler ultrasound to obstetric management. The role of this new technology is, however, less than certain, an early optimism having given way to a more reserved estimation of its potential. It appears that Doppler techniques will undergo a more reasoned assessment than preceding ultrasound applications in obstetrics, namely cardiotocography and real-time imaging.

With the burgeoning number of new recruits to Doppler research it has become clear that there is a major gap in the literature introducing the clinician to the underlying physics and instrumentation. Currently this information is presented as a brief introductory paragraph in clinical articles or in texts which have been prepared for the physicist rather than the physician. Clearly, understanding these fundamentals is essential to obtaining the optimal results, to interpreting these findings, and in developing new applications. This publication goes a considerable way to fulfilling this need.

These authors have a well-established reputation in this field as bioengineers who have seen this technology move out of the laboratory and into clinical practice chiefly in the assessment of the peripheral vasculature. Their experience is manifested in the clear explanation of technical detail which hitherto I have found unfathomable due to turgid prose, poor layout, and distracting formulae.

Here the chapters are well constructed, concise, and clear. The separation of the text into 'essential' and 'advanced' portions is welcomed. This is achieved without any loss of continuity for the novice who might wish to bypass the more complex theorems and discussions. There are chapters on the physics of fluids and ultrasound and systemically on all aspects of signal management from processing to analysis.

Perhaps a fuller chapter on waveform analysis was warranted. This is the area where the greatest advances are to be made yet the authors have not included an examination of the merits and failings of the indices described and only scant detail of pathophysiological correlations. In a later chapter we are given a taste of this latter approach but diluted with an unnecessary repetition of the analytical techniques and specifically concerned with the lower limb. Furthermore, although the authors have prefaced their work by stating that clinical applications will be dealt with superficially, they have also dealt with them unevenly. Unfortunately, little justice is done to the obstetric literature.

But these are minor niggles. The authors have produced a text of manageable size and achieved their aim of providing a technical work which is accessible both to clinicians and physicists. I would recommend this work to all embarking on Doppler research.

G. A. Hackett

Books received some of which may be reviewed at a later date

Effective Care in Pregnancy and Childbirth. Volumes 1 and 2 edited by Iain Chalmers, Murray W. Enkin & Marc J. N. C. Keirse. **Volume 1. Pregnancy** Parts I–V, pages 3–791. **Volume 2. Childbirth** Parts VI–X, pages 792–1516. Oxford University Press, Oxford, 1989, £225.00

Obstetrics edited by Alec Turnbull & Geoffrey Chamberlain. Churchill Livingstone, Edinburgh, 1989, 1200 pages with 542 illustrations, £95.00

Ultrasound and Infertility edited by Asim Kurjak. CRC Press, Inc., Boca Raton, Florida, 1989, 212 pages fully illustrated, £79.50

A Woman's Guide to Birth-Tech. Tests and Technology in Pregnancy and Birth by Anne

Charlish. Christopher Helm, Bromley, Kent, 1989, 168 pages illustrated with line drawings, £4.95

Gynaecological Endocrinology. A Guide to Understanding and Management by Maureen Dalton. Macmillan Press, Basingstoke, 1989, 136 pages illustrated, £25.00

Manual of Gynecologic Oncology by Enrique Hernandez & Neil B. Rosenshein. Churchill Livingstone, New York, Edinburgh, 1989, 184 pages, £17.50

Handbook of Perinatal Infections Second edition by John L. Sever, John W. Larsen & John H. Grossman III. Little Brown & Company, Boston/Toronto, 1989, 300 pages illustrated, £15.95

Natural Family Planning. A Guide to Provision of Services World Health Organization, Geneva, 1988, 82 pages, Sw.fr. 16.00

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